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ROENTGEN THERAPY IN CONJUNCTION WITH THYROIDECTOMY IN THE TREATMENT OF SEVERE HYPERTHYROIDISM

GEORGE CRILE, JR., M.D.

In spite of recent improvements in the preoperative management of patients with hyperthyroidism, there still is a small group of elderly patients in whom thyroidectomy cannot be made safe by medical treatment alone. These cases occur almost exclusively in the older age groups and are characterized by failure of the patient to improve in response to rest and iodine. Loss of weight and appetite occur and persistent mental confusion or delirium with or without elevation of temperature may be present. The liver function, as measured by the bromsulfalein test, is often impaired and the icterus index may rise to 15 or 20. In the past it has been necessary to reject these cases as inoperable.

Pole ligations have long been used as preliminary measures to reduce the severity of the hyperthyroidism and to render the patient operable. The results from pole ligations, however, are by no means uniformly satisfactory. Clinical improvement is noted in about only 50 per cent of all patients in whom ligations alone are performed. In addition, pole ligations performed in bad risk cases always entail a definite hazard, for even this minimal surgical procedure may initiate a fatal thyroid crisis.

Roentgen therapy has long been used in the treatment of hyperthyroidism but in the uncomplicated case, surgery is the treatment of choice. In response to roentgen therapy, the basal metabolic rate frequently will approach normal, the nervousness may subside, and the patient may gain weight. Too frequently, though, the tachycardia will persist and the eye signs may progress. In short, the remissions induced by roentgen therapy, except in early cases of residual or recurrent hyperthyroidism in which there is little or no palpable enlargement of the thyroid, tend to be both incomplete and transitory, as compared with the results obtained by thyroidectomy.

In some cases of diffuse goiter with hyperthyroidism, if the bulk of thyroid tissue is not too large, a definite, although often incomplete and transitory, remission of symptoms takes place in response to roentgen therapy. This remission occurs within a month after the onset of treatment and is most marked in from six to ten weeks after treatment is started. In patients with small diffuse goiters, the results obtained by the use of roentgen therapy are far superior to those obtained in patients with large adenomas.

I do not employ roentgen therapy in the treatment of uncomplicated hyperthyroidism. Too often valuable time is lost and the failure of roentgen therapy to induce a satisfactory remission results in progress of the disease to the point where the operative risk is increased. In the

desperate case, however, where surgery cannot be undertaken because of delirium or other contraindications, roentgen therapy may be of value in diminishing the severity of the disease to such an extent that thyroidectomy can be performed with safety. Roentgen therapy is less hazardous than pole ligation, usually affords greater clinical improvement, and therefore, has supplanted pole ligation as treatment preliminary to thyroidectomy in the occasional bad risk case.

Case Report

The patient was a man sixty years of age whose chief complaint was weakness which had been present for eighteen months. He had lost twenty-five pounds in weight. The pulse rate when at rest in bed was 100 beats per minute and the blood pressure was 150 mm. systolic, 80 mm. diastolic. At entry the basal metabolic rate was plus 57 per cent. He was given 15 minims of Lugol's solution three times a day, a high vitamin, high carbohydrate, high caloric diet, and he was kept at rest in bed. The pulse rate, blood pressure, and basal metabolic rate did not respond to this therapy. At the end of ten days the basal metabolic rate was plus 42 per cent, the pulse rate 100, and the blood pressure 140 mm. systolic, 70 mm. diastolic. Clinically, the patient was much worse. He had lost ten pounds in weight in ten days. He was mentally confused and delirious at night in spite of the fact that all sedation had been withdrawn. The temperature rose to 100.2° F. in the evening. The liver function was impaired, as evidenced by an icterus index of 10, and by 100 per cent retention of dye five minutes after the injection of 2 mg. of bromsulfalein, and five per cent retention at the end of one-half hour. He had lost all appetite and felt nauseated at times. A thyroid crisis was impending; therefore, thyroidectomy was contraindicated.

Roentgen therapy was started on the tenth day after admission and thirteen treatments were given in the next fifteen days. The pulse rate rose to 130 between the third and fifth treatment and the basal metabolic rate rose to plus 56 per cent. A total irradiation of 2300 r units was given to the thyroid area. At the completion of the therapy the appetite had improved, and he had gained three pounds in weight. The basal metabolic rate had fallen again to plus 43 per cent. During this time the dosage of Lugol's solution had been reduced to five minims three times daily. The patient was discharged from the hospital and instructed to continue this same dosage of iodine and to rest in bed at home. He still was mentally confused in the evenings.

The patient returned seven weeks after the first roentgen treatment. His appetite was good and he had gained fifteen pounds in weight. His mind was clear. Although the tachycardia was unchanged and the basal metabolic rate was still plus 34 per cent, he had made a striking clinical improvement. After a few days of preparation with increased dosages of iodine, a left hemithyroidectomy was performed. The patient was placed in an oxygen tent, he was given a blood transfusion, and glucose was administered intravenously by the continuous drip method. In spite of these measures, the operation was followed by considerable reaction, the temperature rising to 104° F. Five weeks later the remaining lobe was removed. There was minimal postoperative reaction and the patient was discharged from the hospital on the seventh postoperative day. He has since regained his lost weight and his pulse rate is normal.

This case illustrates the results that have been obtained in a small group of bad risk cases which have been subjected to roentgen therapy prior to operation.

ROENTGEN THERAPY

It has frequently been stated that roentgen therapy makes the thyroid adherent to surrounding tissues and therefore is contraindicated in patients who are to be subjected to surgical intervention. Adherent glands may be present in some patients who have had roentgen therapy, but this may be equally true of longstanding hyperthyroidism in any patient who has been subjected to prolonged iodine therapy. If roentgen therapy is properly administrated, the thyroid will often be no more adherent than the ordinary exophthalmic goiter. Even if the technical difficulties were increased by the administration of roentgen therapy, this still would be no contraindication to its use. The dangers of thyroid surgery today lie not in the technical hazards of operation, but rather in the physiological problems that arise with the combination of old age and severe hyperthyroidism. Anything that will decrease the severity of the hyperthyroidism will render operation less hazardous and will lower the mortality rate.

The routine use of roentgen therapy as a preliminary preoperative measure would be both economically unsound and physiologically unnecessary. However, in the type of bad risk case that represents 2 or 3 per cent of all cases of hyperthyroidism, and in which pole ligations were formerly performed, the treatment may result in either a lowering of the operative mortality, or a widening of the scale of operability, or both. Since adopting this method of treatment for bad risk cases, we no longer have found it necessary to perform pole ligations.

SUMMARY

1. Roentgen therapy is of value in the preoperative treatment of bad risk patients with severe hyperthyroidism.

2. I do not recommend roentgen therapy for the treatment of uncomplicated hyperthyroidism.

3. Roentgen therapy has taken the place of pole ligation as a preliminary measure in preparing bad risk cases for thyroidectomy.

4. By combining roentgen therapy with stage operations, the mortality rate of thyroid surgery may be reduced and the operability rate increased.

LATE SYPHILIDS OF THE NODULAR AND NODULO-ULCERATIVE TYPE

E. W. NETHERTON, M.D.

The cutaneous manifestations of late syphilis may be divided into (1) solitary gumma and (2) nodular syphilid. The nodular syphilid may or may not become ulcerated; consequently, it is designated a nodular ulcerative or a nonulcerative syphilid. Late syphilids of the palms and soles may be erythematous and scaly and simulate the commoner squamous dermatoses such as psoriasis and epidermophytosis, and therefore will not fit well into this classification of late syphilids. Such a late palmar and plantar syphilid may not show many of the characteristics so consistently observed in late nodular syphilids located elsewhere. However, nodular syphilids may occur on the palm or sole and the squamous syphilids of these areas usually have one or more of the characteristics of late syphilids such as well defined, arciform, indurated margins or grouped indurated papules.

Because syphilis is a disease of protean manifestations, its late systemic effects often are unrecognized. However, the physical characteristics of late nodular syphilids are so distinctive that when certain combinations of these features are present in a lesion they are considered pathognomonic. This enables a physician who is familiar with the morphology of late syphilids to detect the presence of the disease in certain patients without the aid of serologic reactions. The blood serologic reactions of patients with late syphilis frequently are negative, and also individuals with late cutaneous syphilis often do not show other evidence of syphilis such as clinical signs of cardiovascular or neurosyphilis. Therefore, the clinical recognition of a late syphilid may be an important factor in the solution of a puzzling clinical problem.

Two decades ago patients with late syphilids were commonly seen in this clinic. During the past few years, however, late cutaneous syphilis has become relatively uncommon, while during this same period the number of patients with latent and late visceral syphilis has increased. This decrease in the incidence of late syphilids seems to be general. Many young physicians who are completing their training have commented on the small number of cases of late nodular syphilids they have seen throughout their course of undergraduate study. The decrease in the incidence of late cutaneous syphilis is in part probably the result of modern antisyphilitic therapy. In favor of this assumption is the observation that many patients with late syphilids do not know they have the disease or if they do know they are infected they never have received modern antisyphilitic remedies.

The purpose of this presentation is to point out the basic characteristics of a nodular syphilid. As physicians are familiar with the characteristics

of solitary gumma, this form of late cutaneous syphilis will not be considered.

Because of the desire to emphasize the distinguishing characteristics of nodular and nodulo-ulcerative syphilids, a discussion of the differential diagnosis of late cutaneous syphilis has been omitted. All granulomatous processes have characteristics in common with late syphilids and in some cases a clinical differentiation is difficult and at times impossible. However, there is a combination of characteristics common to granulomas that is distinctive of late cutaneous syphilis.

Late syphilids are the result of an intense inflammatory reaction to a local focus of spirocheta pallida. They are an indication of allergy or sensitivity to the organism which is acquired by the host, usually late in the disease. The intense tissue reaction destroys or decreases the virulence of the spirochetes and varying degrees of tissue destruction follow.

Late syphilids are solitary lesions and are not infectious. One or more lesions may be present. They usually are asymmetrical in distribution, and tend to have a characteristic configuration. The lesions are circle-like, irregular or serpiginous in outline and the nodules tend to be arranged in segments of circles. This arciform configuration is an important characteristic of nodular syphilids. The central part of the lesion heals as one or more portions of its well demarcated margin extend peripherally. There is no tendency for new nodules to form in the healed, scarred areas of the lesion. The active parts of the lesion are firm, brownish-red, indurated, smooth, or slightly scaly nodules which are seen at the actively spreading margins. The nodules may remain discrete or coalesce to form an arciform, indurated, advancing segment of the periphery of the lesion. Some nodules break down and are replaced by rounded or irregularly punched-out ulcers with indurated straight margins. As these ulcers heal, the resulting scar is thin or atrophic, noncontractile, and usually surrounded by a hyperpigmented areola. This atrophic scar is a significant characteristic of late cutaneous syphilis. Some degree of atrophy may occur in the absence of ulceration. The atrophic scars retain the arciform arrangement of the original lesions and the peripheral hyperpigmentation persists for many months. This type of scar is of diagnostic importance and should not be dismissed lightly when observed during the course of the examination. In some patients, scarring may be the only clinical evidence of late syphilis. Therefore, the physician should carefully examine all cutaneous scars.

The most significant characteristics of late nodular syphilids are the arciform configuration of the lesion, the induration, and the atrophic noncontractile scar surrounded by a zone of hyperpigmentation.

The following cases illustrate the characteristics of late nodular syphilids:

Case 1: A married man came to the Clinic in September, 1936, complaining

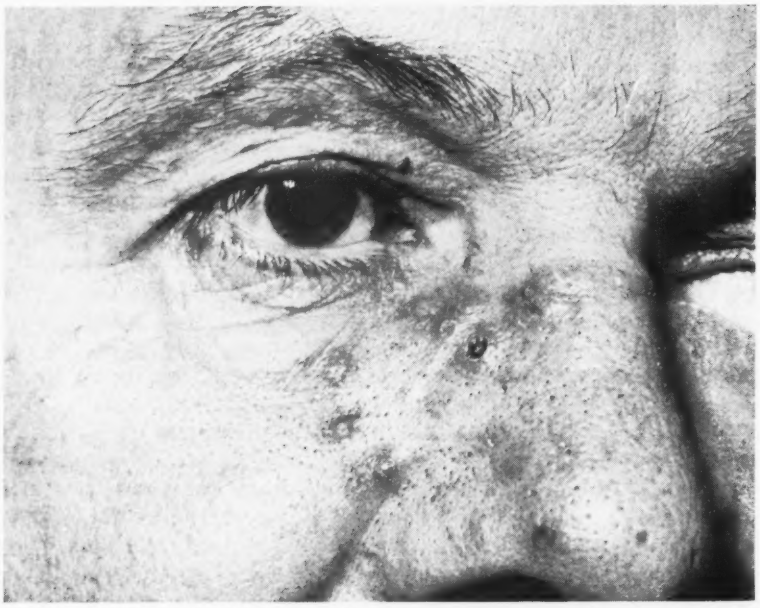


FIGURE 1: Solitary ringed lesion with indurated, brownish-red nodules at the periphery. Active portion of lesion is below the eye. The healed and involuting portion is on the nose. Note the tissue destruction with ulceration and crusting of one nodule.

of an eruption on the face, nervousness, and lack of endurance. During the past year he had become nervous and irritable, and he tired easily. These symptoms increased in severity and recently he had slept poorly and had lost his appetite.

In the fall of 1935, a "pimple" appeared on the right side of the nose. This lesion enlarged by peripheral extension and by January, 1936, several dull red nodules developed just below the eye on the right side of the face. One nodule near the inner canthus of the right eye interfered with his wearing glasses. A central crust developed on some of the lesions.

Treatment at that time consisted of one treatment with ultraviolet light and the application of ointments, but the lesions did not improve. Since adolescence there had been numerous comedones and an occasional acne on the face. With the exception of the eruption on the face and a slight bilateral nerve deafness, physical examination showed no abnormal findings.

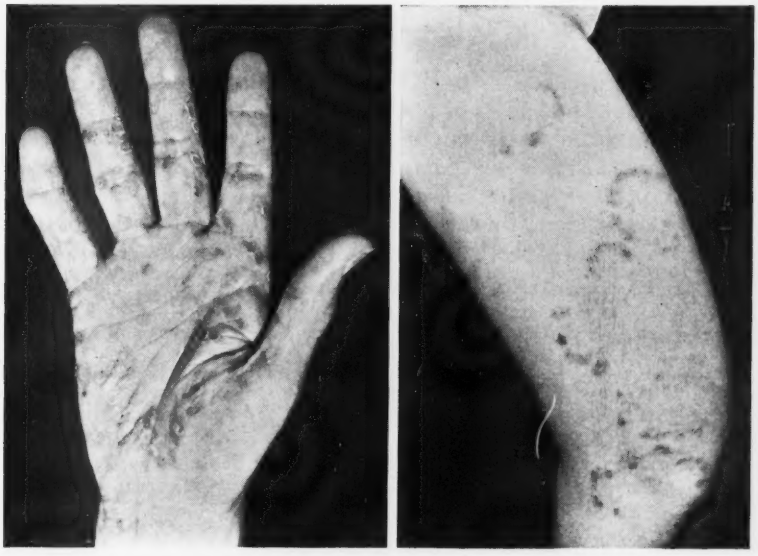
The skin of the face was abnormally oily and numerous comedones were present on the nose. Small, indurated, brownish-red cutaneous nodules were located only on the right side of the face and nose (Fig. 1). The lesion as a whole was circinate. The nodular and nodulo-ulcerative lesions were at the periphery. The nodules on the right ala and distal portion of the nose had almost disappeared, but those on face and near the base of the nose were more active. This portion of the periphery was arciform and was the progressive portion of the lesion. A sharply demarcated and infiltrated margin was present across the ridge of the nose at its base. Atrophic scarring was not conspicuous. There was slight atrophy near the lateral portion of the lesion.

Wassermann and Kahn tests of the blood gave strongly positive reactions. Blood counts and urinalysis showed normal findings. Examination of spinal fluid revealed 51 lymphocytes per 100 cc., a faint trace of globulin, a total protein of 25 mg. per 100 cc., a 4 plus Wassermann reaction, and a negative gold chloride reaction.

Comment: This patient had a late nodulo-ulcerative syphilid on the face and associated syphilis of the central nervous system. He was nervous and irritable but came to the Clinic primarily for the cutaneous eruption which had failed to heal following the use of topical remedies. With the exception of a slight bilateral nerve deafness, there were no neurologic signs which would suggest that this patient had neurosyphilis.

This case demonstrates the value of the recognition of a late syphilid as a diagnostic aid and the importance of including examination of the spinal fluid in the investigation of a patient who is known to have or who is suspected of having syphilis.

Case 2: A fifty-nine year old woman came to the Clinic in June, 1939, because of an eruption on the arms and the right palm. For the past five years recurrent groups of red "spots" had appeared on the arms and the right palm, the lesions being more numerous on the left arm. The eruption would last for a few weeks or months and then would disappear almost completely, only to return without any apparent reason. There had been no itching and at no time had vesiculation



2A 2B

FIGURE 2: A. Lesion consists of infiltrated, smooth or scaly brownish-red papules surrounded by a collarette of loose epithelium. They are grouped and in places have an arciform arrangement. No vesicles or pustules are present.
B. Brownish-red nodules arranged in an arciform configuration. Induration of the skin is a prominent characteristic.

or ulceration of the lesions been present. She had not been well for several years but had no particular symptom or group of symptoms. Antisyphilitic treatment had never been given, and she had not suspected that she might have syphilis.

Physical examination showed no noteworthy findings except for the eruption on the right hand and arms. An eruption was seen on the right palm and on the lateral and palmar surfaces of the fingers (Fig. 2A.) The left palm and the feet were not involved. The eruption consisted of large, brownish-red, flat, smooth and indurated papules which were arranged in groups, and in an arciform configuration which was seen best in the area between the thenar and hypothenar portions of the palm. There was distinct induration of this margin of the lesion and its surface was slightly scaly. Many of the papules were surrounded by a collarette of loose epithelium.

The eruption on the left arm consisted of brownish-red nodules arranged in an arciform configuration (Fig. 2B). Some of the nodules formed segments of circles while others were arranged to produce a serpiginous outline to a large circle-like lesion. The nodules were smooth or were covered with thin and loosely adherent scales. Deep induration could be detected easily by palpation. There were no ulcers. Slight atrophy was present within the central portion of the lesion. Wassermann and Kahn tests of the blood gave strongly positive reactions. The hemogram showed a mild secondary anemia. The spinal fluid was normal.

The lesions disappeared under antisyphilitic treatment with intramuscular injections of bismuth salicylate, and potassium iodide by mouth.

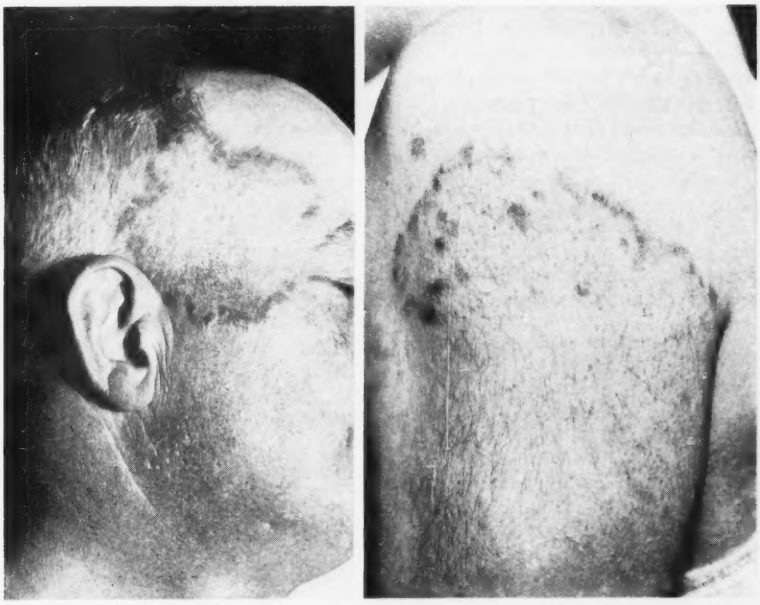
Comment: The arciform configuration and the induration of the lesions on the arms comprise the most important basic physical characteristics of late nodular syphilids. The eruption on the palm is a typical example of late palmar syphilis. The lesion was unilateral, involving the hand which was used most frequently. The indurated papular lesions showed the grouping and arciform arrangement which is typical of late syphilis. The absence of vesicles, and the presence of the induration are two factors against the diagnosis of a ringworm infection which is a superficial erythematous and vesicular eruption.

Case 3: A married man fifty years of age came to the Clinic in May, 1939, complaining of an eruption which had been present for a year. He had gonorrhea when twenty-seven years of age, but denied ever having acute syphilis. He had never received antisyphilitic treatment.

The first lesion was a dull red, raised area on the right temple. There were no subjective symptoms. This lesion enlarged by peripheral extension and cleared at the center at the same time. Two months before coming to the Clinic a similar lesion developed over the deltoid region of the left arm. This lesion also had enlarged by peripheral extension. He had been told that the eruption was a ringworm infection and various ointments and lotions had been applied without any benefit. Except for the cutaneous lesions, the physical examination showed normal findings.

There was a large ringed or circinate lesion in the temple region (Fig. 3A). The margin of the lesion was irregular or serpiginous and was composed of brownish-red nodules. The nodules were fairly discrete in places while in other portions they had coalesced to form a band-like, indurated and elevated margin. There was only slight scaling at some parts of the periphery of the lesion. The skin in

the central portion of the lesion was smooth and showed some atrophy. No atrophic noncontractile scars were seen.



3A 3B

FIGURE 3: Solitary, ringed lesion on temple (A) and an arciform lesion on the arm (B). The margins are nodular or indurated. There is central healing with peripheral extension.

On the deltoid region of the left arm there was a large lesion consisting of brownish-red nodules arranged in an arciform configuration (Fig. 3B). The lesion had enlarged by peripheral extension and the skin beneath the progressing periphery showed some atrophy. Induration of the margins could be detected by palpation. Wassermann and Kahn tests of the blood gave positive reactions. The patient would not submit to a lumbar puncture.

Comment: In this case, the eruption consisted of two solitary lesions of asymmetrical distribution, each lesion consisting of brownish-red, granulomatous nodules arranged in circular and arciform configurations. There was distinct induration, and as the lesions enlarged by peripheral extension, there was central clearing with slight atrophy of the skin.

Case 4: A married man twenty-six years of age came to the Clinic in October, 1935, because of an eruption on the arms and legs. It had been present for three years.

He had acute gonorrhea when twenty years of age, but did not remember having had a chancre or secondaries. Soon afterward he had a positive blood Wassermann reaction. He neglected to take antisyphilitic treatment at that time and had not received any since then.

In 1932, approximately three years after he contracted gonorrhea, a "sore" appeared on the lateral surface of the left leg. This gradually healed, leaving a thin scar. Since then new lesions appeared from time to time near the site of the original "sore." These ulcerated and disappeared, leaving scars. A similar eruption developed on the lateral surface of the right leg and the inner surface of the right elbow. No attempts had been made to cure this eruption.

Except for the cutaneous lesions, physical examination showed normal findings. Wassermann and Kahn tests of the blood gave strongly positive reactions. He would not submit to a lumbar puncture.

There were three solitary lesions, one on the lateral surface of each leg, and one on the inner surface of the right elbow. All lesions showed the same physical characteristics. The lesion near the right knee consisted of a group of atrophic, noncontractile scars, each surrounded by a zone of hyperpigmentation (Fig. 4). These scars were surrounded by punched-out ulcers with granulomatous bases and brownish-red nodules, some of which were covered with adherent scales and thin

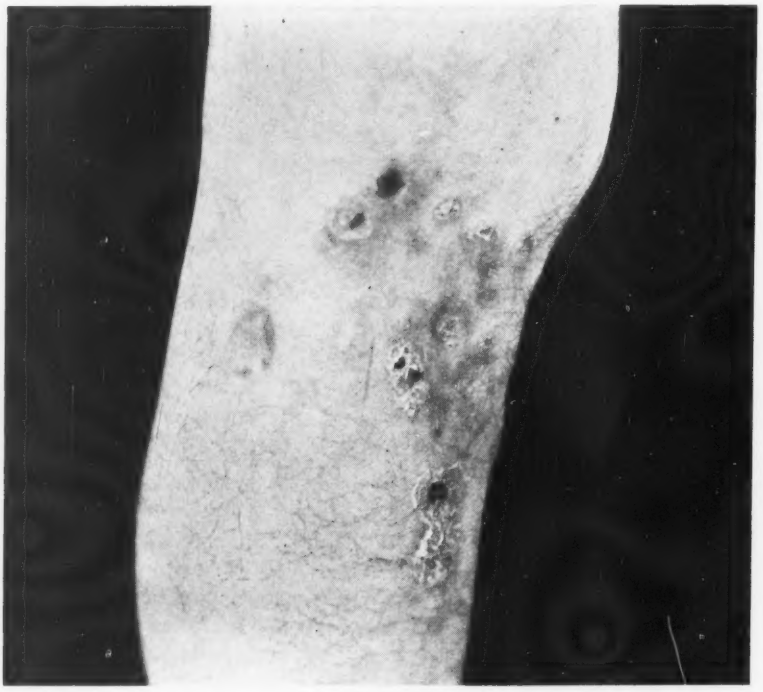


FIGURE 4: Advancing arciform, nodulo-ulcerative portion of the lesion at the upper margin. Atrophic scarring with peripheral hyperpigmentation at right portion of the lesion.

crusts. The nodules and ulcers which comprised the active extending portion of the lesion were located at the periphery and were arranged in an arciform configuration. Palpation of the nodules showed induration caused by the inflammatory reaction in the deep portions of the skin.

Comment: The eruption in this case presented the basic physical characteristics of late nodulo-ulcerative syphilids. The lesions were asymmetrical, few in number, or solitary. They were indolent and the nodules and ulcers were arranged in an arciform configuration at the actively spreading margin. Tissue destruction was evidenced by punched-out ulcers, resulting in atrophic scars which were surrounded by hyperpigmentation and located at the central healed portion of the lesion. Induration of the involved skin, a significant characteristic, could be made out by palpation of the nodules. The duration of the infection was not known; however, this patient was younger than most individuals who have late syphilids.

Case 5: A tailor sixty-three years of age came to the Clinic in May, 1940, complaining of an eruption on the right hand, which had been present for two years. He had been married for twenty-eight years. His wife and two children were living and well. He had gonorrhea when he was twenty-three years of age, but denied having had a chancre or secondary syphilis. He had not suspected that he might have syphilis.

The eruption started on the sides of the right thumb and the thenar aspect of the right hand, as red, scaly and crusted areas. Later lesions appeared on the radial aspects of the right palm, and on the dorsal surface of the hand near the base of the thumb. The lesions had continued to come and to disappear, leaving thin scars. There were no subjective symptoms. Roentgen therapy and the application of ointments had been of no benefit.

Except for the cutaneous lesion, the physical examination showed no abnormal signs.

The eruption was limited to the right hand and involved the thumb, the palm, and the dorsal surface of the hand at the base of the thumb (Fig. 5). It consisted of groups of discrete and coalesced brownish-red nodules arranged in an arciform configuration which was best demonstrated on the thenar aspect of the palm. Here the nodules had coalesced to form a sharply demarcated, advancing, indurated, orbicular or arciform margin. A large adherent scale or thin crust was present on the surface of most of the nodules. There was distinct atrophic scarring of the skin on the dorsal surface of the hand and on the thenar portion of the palm at sites of previous nodules. The tip of the thumb was involved and the thumb nail was thickened, not friable and brownish in color. Nodules had not recurred in the healed portion of the lesion. Wassermann and Kahn tests of the blood were strongly positive.

This eruption had been considered to be a ringworm infection, but the tissue destruction with resulting atrophic scarring and the arciform, advancing, indurated margins are characteristics seen in late syphilids and not in epidermophyton infection. This combination of characteristics are distinctive of late syphilid.

Case 6: A married man fifty-six years of age was first observed in May, 1940. While being examined as a possible donor for his wife who had entered the hospital for a major operation, it was discovered that the Wassermann and Kahn tests of his blood gave strongly positive reactions. For the past two years crusted and ulcerated lesions had been present on the forehead and left elbow. Various ointments had been advised by his physician and the eruption apparently had not improved. However, new crusted areas continued to develop. He had

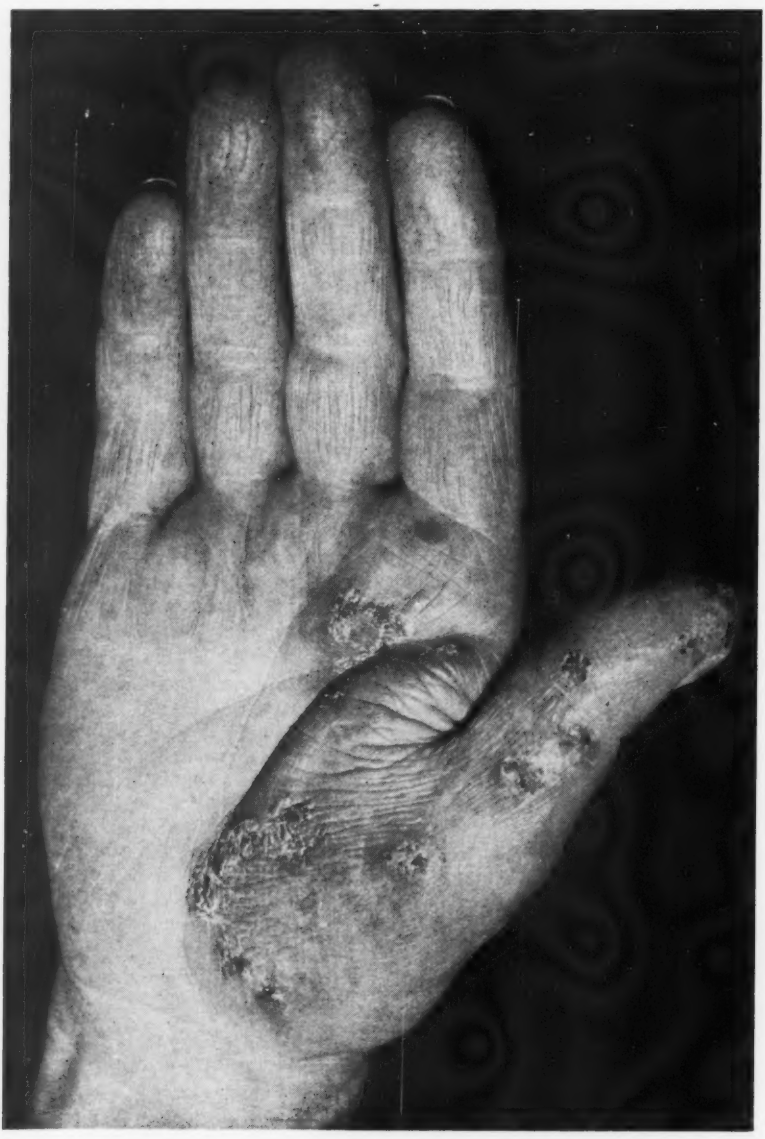


FIGURE 5: Note the grouping and arciform arrangement of the nodules; also atrophy on the thenar eminence.

not suspected that he might have syphilis. He contracted gonorrhea when twenty-six years of age, but denied having had a chancre or secondary syphilis. This was

the first time he had had a blood test and he never had received antisyphilitic treatment.

The initial lesion appeared late in 1938 as a nodule on the left elbow. It was excised but soon afterward new nodules developed near the site of the original lesion. Since then, nodules and ulcers had continued to come and go, leaving scars and hyperpigmentation. For almost two years a smaller but similar erup-

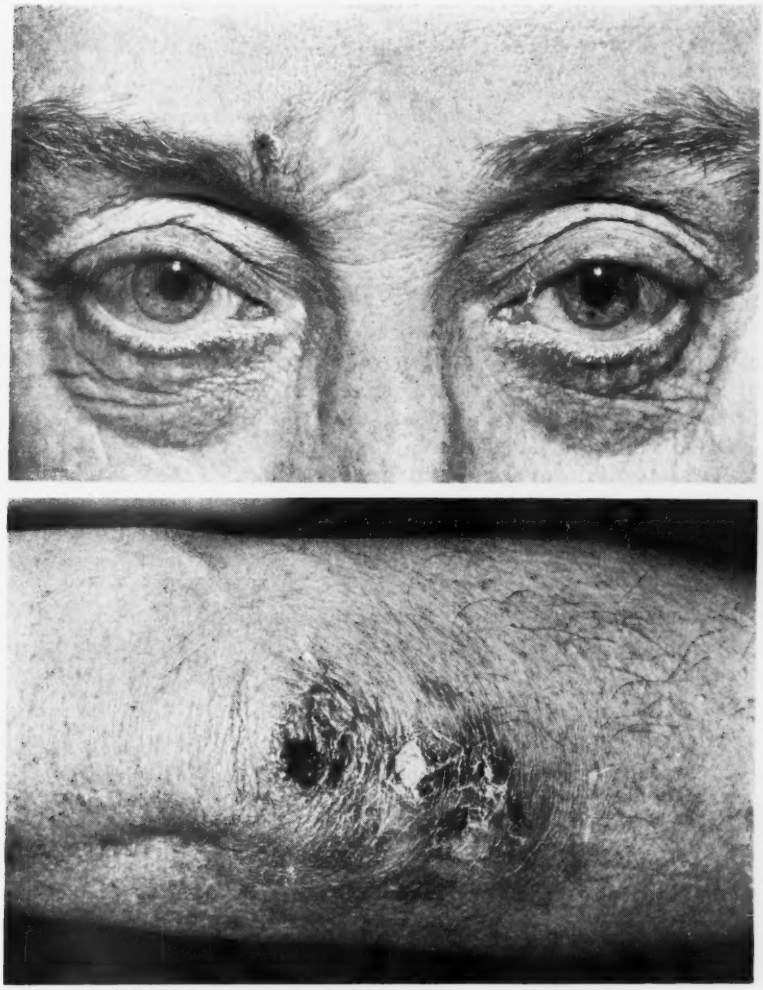


FIGURE 6: Atrophic scarring between the eyebrows and a crusted, involuting granulomatous nodule at its periphery. There are nodulo-ulcerative lesions on the elbow. Also atrophic scars with peripheral hyperpigmentation. Palpation of the nodules showed induration.

tion had been present between the eyebrows. There had been no subjective symptoms.

Physical examination showed a mild hypertension but no abnormal neurologic signs or clinical evidence of cardiovascular syphilis. The hemogram showed a mild secondary anemia and the Wassermann and Kahn tests gave strongly positive reactions. The spinal fluid was normal. There were two solitary cutaneous lesions, one on the left elbow and one between the eyebrows (Fig. 6). A sharply marginated or punched-out ulcer was present over the olecranon process of the left ulna. Immediately below this ulcer were atrophic noncontractile scars and brownish-red smooth nodules. The indurated nodular components of the lesion were located at the periphery. The lesion between the eyebrows consisted of a group of small atrophic scars which were so closely placed as to form one larger, thin, noncontractile scar. At the periphery of this scar and near the inner portion of the right eyebrow there was a partially healed, indurated, crusted, ulcerated nodule. These lesions were typical late nodulo-ulcerative syphilids. The induration, ulceration, peripheral extension with central healing and resulting atrophic scars are basic characteristics of late syphilids. The arciform configuration in the second and third cases was not so apparent in this case.

Summary

The cutaneous lesions seen in these cases illustrate the physical characteristics of late nodular syphilids. They were sufficiently characteristic to be considered pathognomonic and ranked in diagnostic importance with the serologic reactions. In each case, the cutaneous lesions were solitary, indolent and inflammatory. They were circular, serpiginous, or arciform and one or more portions of the margins were nodular, ulcerated, or indurated and tended to advance slowly. As the lesion enlarged by peripheral extension, there was central healing with or without scarring. Tissue destruction occurred frequently. Ulceration resulted in atrophic, noncontractile scars surrounded by hyperpigmentation. In the absence of ulceration, healing resulted in varying degrees of atrophy of the skin which could be detected by careful inspection of the lesion.

The correct interpretation of a cutaneous lesion of this type is very important, particularly if it occurs in a patient who has negative serologic reactions. It may be the clue that leads to the solution of a difficult clinical problem, or as demonstrated in Case 1, may lead to the discovery of a more serious unsuspected manifestation of syphilis.

RETROPULSION OF RUPTURED NUCLEUS PULPOSUS SIMULATING TUMOR OF THE CAUDA EQUINA

Report of a Case

A. T. BUNTS, M.D.

During the past three years at the Cleveland Clinic more than sixty patients, whose preoperative diagnosis was ruptured intervertebral disc, have revealed such a lesion at operation. In all but two of these cases the lesion occurred in the lumbar spine. It usually was situated on one side only, impinging on a single nerve root, and causing low back pain with radiation into one leg. The clinical impression was confirmed in each case by contrast myelography before resorting to operation. In only one case, the subject of this report, was a definite preoperative diagnosis of tumor of the cauda equina made and firmly adhered to until laminectomy revealed a large ruptured fragment of the nucleus pulposus of the intervertebral disc between the third and fourth lumbar vertebrae. Because of the interesting and confusing characteristics of this case, it is reported below.

CASE REPORT

History: A married white woman, thirty-five years of age, first noticed pain in the lumbar spine and in both hips five or six years previously. The pain occurred most frequently while the patient was in the sitting position. It was intermittent, recurring at intervals. Following the birth of a baby eighteen months prior to examination, there was a marked exacerbation of pain in the lower back and in both hips, with aggravation of the pain on coughing and sneezing. For six months prior to examination the symptoms gradually became more troublesome. During the last six weeks the pain became severe and was accompanied by marked weakness of the legs, inability to move the toes of the right foot and the right ankle, and numbness and tingling of the feet and saddle area. The pain shifted from one hip and thigh to the other. She received injections for "neuritis." There was bowel incontinence on one occasion, but no loss of vesical sphincter control.

Examination: The general physical condition of the patient was excellent. Neurological examination revealed marked weakness of both legs with a foot drop on the right side. The patellar reflexes were equal and active. Both Achilles reflexes were absent. There was a peculiar disorder of sensation with hyperesthesia and paresthesia over the entire right leg from the hip down and over the left leg below the knee. There was no definite hypesthesia or anesthesia. The anal reflex was intact.

Roentgen examination of the lumbosacral spine showed no abnormality other than slight narrowing of the intervertebral space between the third and fourth lumbar vertebrae, and sacralization of the fifth lumbar vertebrae on the left side. The width of the spinal canal was normal.

Lumbar puncture between the fifth lumbar vertebra and the sacrum obtained only one or two cc. of clear yellow fluid which quickly clotted in the test tube.

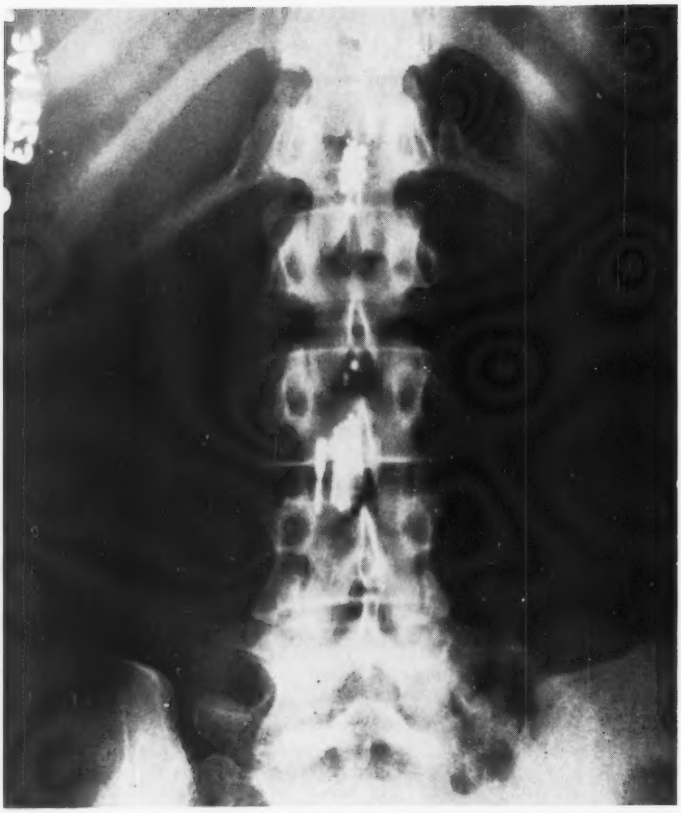


FIGURE 1: Contrast myelogram of the lumbar spine showing complete block of lipiodol at the upper part of the third lumbar vertebra.

There was no response to jugular compression, indicating a complete spinal subarachnoid block. The fluid contained 3,500 mg. of total protein per 100 cc.

Cisternal puncture showed clear, colorless fluid under normal pressure, containing 35 mg. of total protein per 100 cc. An injection of 1 cc. of heavy lipiodol was made into the cisterna magna. Roentgen studies of the spine revealed that the descent of the oil was completely blocked at the level of the upper part of the third lumbar vertebral body (Fig. 1), even after the patient had been lying for twenty-four hours with the head of the bed markedly elevated.

The preoperative diagnosis was tumor of the cauda equina.

Operation: Laminectomy of the second, third, fourth, and fifth lumbar vertebrae was carried out. The laminae and pedicles showed no pressure atrophy. The ligamenta flava were normal in thickness. The posterior aspect of the dura was normal. The dura and the arachnoid were opened in the midline throughout the length of the exposure. The strands of the cauda equina showed no abnormal change other than an apparent extravasation of blood in one nerve sheath, although

the bundle of nerves seemed to be displaced posteriorly opposite the third lumbar vertebral body. Above this level, droplets of lipiodol seemed to be captured in the meshes of the arachnoid and were removed by manipulation, irrigation, and aspiration. There was no evidence of an intradural tumor, but when the bundle of nerves was retracted gently to one side at the level of the third lumbar vertebral body, a smooth posterior bulging of the anterior dura about 1.5 inches long was seen. Palpation through the dura showed the mass to be soft and elastic. The mass was much longer and wider than that usually seen in a ruptured intervertebral disc. It extended across the entire width of the spinal canal, causing marked compression of the dural sac and its contained cauda equina. The operator considered it to be an extradural neoplasm. A linear incision 1.5 inches long was made through the dura overlying the mass, and at once an irregular, white, shaggy mass of tissue partially extruded itself through the dural opening. It had the gross appearance of fibrocartilage and was thought to be a ruptured nucleus pulposus. By careful blunt dissection the unusually large mass was removed entirely through the dural opening. It had arisen from the intervertebral disc between the third and fourth lumbar vertebrae and apparently had forced its way upward in the spinal canal between the anterior dura and the body of the third lumbar vertebra. Its only remaining attachment to the interior of the intervertebral disc was by a fine strand of fibrocartilage. The operator was unable to determine whether or not there was a complete rupture of the posterior longitudinal ligament. The anterior dural opening was closed with interrupted silk sutures and the posterior dural opening was closed with a continuous silk suture. The muscles, fascia, and skin were closed in the usual manner.

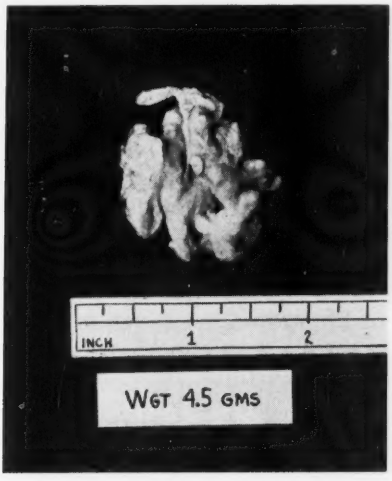


FIGURE 2: Ruptured nucleus pulposus removed in this case.

Pathological report: The specimen consisted of an irregular, white, shaggy, elastic piece of tissue, weighing 4.5 grams and measuring 1.5 inches in its longest dimension (Fig. 2). The histological picture was characteristic of fibrocartilage.

At the time of this report, two weeks after operation, the patient is making an uneventful and satisfactory recovery in the hospital. She is free from her former

pain. Motor function of the left leg is good, but the right leg still is weak, although somewhat stronger than before operation. Return to normal function will undoubtedly be gradual over a period of months.

Discussion

A thorough consideration of the history and the neurological signs in this case, with the yellow color and high protein content of the cerebrospinal fluid, the presence of a complete spinal subarachnoid block by Queckenstedt's test, and a complete block of lipiodol at the level of the third lumbar vertebra would certainly justify the diagnosis of a tumor of the cauda equina. In no other case of ruptured intervertebral disc observed at the Cleveland Clinic has a complete spinal subarachnoid block been found by Queckenstedt's test and by lipiodol myelography. In every other case the cerebrospinal fluid has been colorless and the total protein content has not exceeded 195 mg. per 100 cc. In 30 per cent of the cases the total protein content has been below 40 mg. per 100 cc. and has rarely exceeded 100 mg. in the remaining cases.

Following operation an attempt was made to obtain a more detailed chronological history of symptoms from the patient in order to bring out points which might have caused us to suspect a possible ruptured intervertebral disc. She emphasized the intermittency of the pain over a period of five or six years and stated that five weeks prior to her visit to the Clinic there had been a rather sudden exacerbation of severe pain in the lower back, both hips and thighs. This occurred when she attempted to change her position in bed by grasping the head of the bed with her hands and pulling her body upwards. Almost immediately she began to notice weakness and numbness of the legs. There probably had been a partial retropulsion of the intervertebral disc for several years, giving rise to intermittent symptoms. The annulus fibrosus and the posterior longitudinal ligament may have become thinned out by years of pressure until slight, indirect trauma suddenly caused the nucleus pulposus to break through these atrophic structures and extrude itself into the spinal canal. The mass of fibrocartilage was unusually large, weighing four times as much as the average mass of tissue removed in cases of ruptured intervertebral disc seen at the Cleveland Clinic. The extrusion of such a large mass into the spinal canal caused a pronounced posterior dislocation of the dural sac, with compression of the cauda equina and complete obstruction of the subarachnoid space. Thus, it may be possible to explain the mechanism by which such a lesion could give rise to a clinical picture closely simulating that of a tumor of the cauda equina.

TUMORS OF THE TRACHEA

HAROLD E. HARRIS, M.D.

The development of the bronchoscope has aided much in the early and accurate diagnosis of tumors of the trachea. Prior to its common use, a tumor of the trachea usually was an incidental finding at necropsy, except for the occasional tumor found by indirect laryngoscopy. Reports of tracheal tumors have become progressively more frequent with improved methods in laryngoscopy and bronchoscopy and with more complete postmortem studies.

In 1929, D'Aunoy and Zoeller[1] presented an exhaustive survey in a report of 351 cases of tumors of the trachea. Culp[2] in a review of all the reported cases over a seven year period from 1929 to June, 1936, found eighty-two new cases of primary tumors, fifty-six of this number being described as carcinomas. Of the total 443 primary tumors reported, 147 or 34 per cent were carcinomas.

Tumors of the trachea usually are classified according to the pathological picture but some prefer to classify them according to their relationship to the tracheal wall, namely, endotracheal, murotracheal, and peritracheal. They may be obstructive or nonobstructive, and may be located in the cervical trachea or in the intrathoracic trachea. The lumen of the trachea is more than ample to supply the required air, for its area of cross-section is more than twice that of the widely open glottis. Therefore, very small growths may not give signs of tracheal obstruction.

Endotracheal tumors obstruct the lumen of the trachea by their bulk, and murotracheal and peritracheal growths obstruct the lumen by crowding the wall inward. Jackson[3] states that a tumor situated in any of the three areas mentioned above may cause one of four types of valvular obstruction: (1) stop-valve obstruction in which air cannot pass in either direction; (2) by-pass valve obstruction in which the air can pass both in and out in diminished quantity; (3) check-valve obstruction permitting the ingress but not the egress of air, producing emphysema of both lungs; and (4) check-valve obstruction permitting air to escape from the lung but preventing ingress, to produce atelectasis. If obstruction is complete, asphyxia occurs promptly.

Another mechanism of obstruction is paralysis of the recurrent nerve. If the involvement is unilateral, no dyspnea will result except on exertion. In most instances there is some phonatory impairment for a time, but occasionally the voice is not affected. One or both vocal cords may be paralyzed by a tracheal tumor which produces no other sign or symptom of its presence. This is especially true when the tumor involves the posterior tracheal wall.

Although almost every conceivable type of tumor has been reported

in the region of the trachea, the most common peritracheal tumor is goiter. The most common endotracheal tumor is papilloma, carcinoma being next most frequent. Other tracheal tumors include adenoma, fibroma, myoma, angioma, hematoma, myxoma, fibrolipoma, fibromyxoma, lymphoma, ecchondrosis, ecchondroma, osteophytoma, osteoma, retention cysts, chrondroma, tophus, dermoid cyst, aberrant thyroid, thymus, gumma and the chronic granulomatous lesions. The most common malignant tumor in the trachea is carcinoma, next in frequency is sarcoma, and least in frequency is endothelioma. Probably because of the greater abundance of glandular structures, tracheal tumors are located more frequently on the posterior wall than on the anterior wall and more frequently on the lower third than the upper third.

The most important early symptom is a wheeze heard at the open mouth. The asthmatoid wheeze, so called by Jackson[4] because of similarity in sound, usually is present for some time before dyspnea, the next important symptom, develops. Nocturnal paroxyms of dyspnea often are caused by the accumulation of secretions around and below the tumor. When the size of the tumor is sufficient to encroach upon the lumen, a wheeze is produced, the dyspnea becomes constant, and the nocturnal paroxysms are more severe. A chronic mucoid productive cough may occur which may be either very mild, or there may be strangling paroxysms relieved only by coughing up the secretion. Hemoptysis frequently is associated with adenoma. Fever from necrosis of the tumor itself or pulmonary suppuration secondary to the tracheal obstruction may be present.

Diagnosis

The symptomatology is not sufficient for a diagnosis, although a history of wheezing and nocturnal attacks of dyspnea should make one suspect a tracheal tumor.

The physical signs in uncomplicated, nonobstructive tracheal tumors are negative, but with the slightest degree of obstruction, they are definite and of great importance. The earliest physical sign of tracheal obstruction is a wheeze heard at the open mouth. Next in importance are signs of by-pass valve obstruction, chiefly harsh breath sounds and later check-valve obstruction, producing atelectasis and emphysema distal to the tumor. There is also retraction of Burns' space and the intercostal muscles on inspiration. When atelectasis or emphysema are present, a tracheal tumor should be placed first among the diagnostic possibilities.

If the roentgen examination of the chest does not reveal small endotracheal tumors, or if the tracheal wall does not stand out clearly with a negative shadow showing the lumen, the outline may be more clearly

visualized by the insufflation of bismuth subcarbonate or the instillation of lipiodol.

The only positive method of establishing the presence of an endotracheal tumor or of compression caused by a peritracheal tumor is by bronchoscopic examination. The type of tumor usually can be determined by bronchoscopic biopsy. The presence and frequently the kind of tracheal tumor above the level of the suprasternal notch can be determined by palpation.

Nocturnal paroxysms of dyspnea from an accumulation of secretions around and below the tumor contribute to the diagnostic difficulties. The most common erroneous diagnosis for a tracheal tumor is asthma. The thymus and thyroid glands frequently have been blamed for obstruction which they were not producing, and heart failure has been blamed for wheezing which did not subside on bed rest and digitalis.

Treatment

Benign endotracheal tumors of limited extent require only bronchoscopic removal, which will be curative except for the multiple papillomas which tend to recur locally and elsewhere in the respiratory tract. These are best treated by superficial removal repeated frequently enough to keep the lumen open. Fibromas and hemangiomas usually are best treated by electrocoagulation, care being taken not to damage the tracheal cartilage. Malignant endotracheal tumors are best treated by roentgen therapy. Peritracheal tumors, when benign, usually can be removed surgically, especially those in the cervical region. Roentgen therapy usually is the treatment of choice in the malignant peritracheal lesions.

Prognosis

Benign tracheal tumors are fatal primarily by producing asphyxia or secondarily by causing suppuration in the lungs. If a benign endotracheal tumor is removed bronchoscopically, the prognosis is good. Recurrence is more common in the cases of papilloma. The prognosis of benign adenoma is good but any recurrence should be treated early.

Summary

The symptoms of a tracheal tumor closely resemble those of asthma: wheezing respiration, nocturnal attacks of dyspnea, and dyspnea on exertion. In the case of tracheal tumor, asphyxia is almost a certainty unless averted.

The dyspnea may be due to recurrent nerve paralysis, endotracheal tumor, or compressive peritracheal tumor. These may be differentiated by direct laryngoscopy and bronchoscopy.

The diagnosis of asthma should be made with great caution, even though the patient has other signs of allergy. If a wheeze can be heard at the open mouth, bronchoscopy will eliminate the possibility of tracheal tumor.

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THE SURGICAL TREATMENT OF PRIMARY CARCINOMA OF THE LUNG

Report of an Unusual Case

T. E. Jones, M.D., John R. Paxton, M.D., and
H. Scott Van Ordstrand, M.D.

Studies during recent years have shown that primary carcinoma of the lungs actually is occurring more frequently. The importance of early diagnosis, followed by early treatment, cannot be stressed too greatly. Surgery is the treatment of choice. The management of the patient with primary carcinoma of the lung entails close cooperation between the internist, the bronchoscopist, and the surgeon.

Incidence: Necropsy studies have revealed the lung to be a far more common site for the development of a primary malignant growth than has been appreciated previously. In a group of 7,685 consecutive necropsies done at the Cleveland City Hospital, and reported by Koletsky[1], the lung was the second most frequent site of origin of primary malignancies, being exceeded only by the stomach. It has been shown that approximately 10 per cent of all primary cancers originate in the lungs. Simons[2] showed that the high incidence of lung cancer today is due to a relative and an absolute increase in frequency. Dublin showed that approximately 150,000 persons die from all types of cancer in the United States each year. This would indicate an average death rate of approximately 15,000 people each year from primary cancer of the lungs in this country.

In a five month period (February 1 to July 1, 1940) thirteen proved cases of primary carcinoma of the lungs were seen at the Cleveland Clinic out of 347 patients presenting respiratory symptoms. As over half of these 347 patients were below the considered cancer age limit, this would suggest a relatively high clinical incidence of primary neoplasms of the lung.

Pathology: It has been shown that between 75 and 90 per cent of all primary carcinomas of the lungs are bronchogenic, the remainder being peripheral. The general consensus of opinion is that all primary carcinomas of the lungs arise in the basal layer of the bronchial epithelium, regardless of whether the site of origin is in the main stem bronchi, or in the terminal bronchioles[3]. The degree of differentiation of this parent cell determines whether or not the tumor will be a squamous cell carcinoma, an adenocarcinoma, or an undifferentiated round cell, spindle cell, or oat cell type of carcinoma.

Symptomatology: The symptoms depend upon the location of the tumor and the degree of involvement. There is no one classical symptom complex in carcinoma of the lungs. In many of the patients the clinical picture simulates a lung abscess, there being bouts of fever with productive cough. The majority of patients eventually complain of pain in the chest, which, to some degree, is a characteristic feature. Cough commonly is an early symptom, as the majority of tumors are centrally located and produce early bronchial irritation. The sepsis in many cases is due to the obstructed area of suppurative pneumonitis. Hemoptysis, caused by ulceration of the neoplasm, is a frequent symptom in the later stages.

Diagnosis: The physical signs depend entirely upon the location of the tumor and the degree of obstruction of the lung tissue. There is no typical roentgen configuration in carcinoma of the lungs. Any parenchymal shadow in the adult lung which cannot be diagnosed otherwise should be considered a carcinoma until disproved. With few exceptions, the shadow seen on the roentgenogram in a case of carcinoma of the lungs is not of the tumor itself but of the area of secondary obstructive pneumonitis. In only a few cases can the tumor be visualized. Roentgenographically, carcinoma of the lung has been shown to simulate almost all other disease processes. The ulcerating form commonly is confused with tuberculosis and lung abscess.

Bronchoscopic examination is the most important single aid in the diagnosis of primary carcinoma of the lungs. Studies have shown that in over 75 per cent of the cases the tumors are so situated in the major bronchi that they can be visualized, and biopsies obtained through the bronchoscope. Bronchoscopy is the best means of making the diagnosis early, as this has been accomplished in a considerable number of patients even before roentgen changes were apparent.

Aspiration lung biopsy has been condemned by some workers, but in a small percentage of cases in which peripheral tumors cannot be visualized bronchoscopically, this procedure is warranted, particularly when it is felt that exploratory thoracotomy would otherwise be necessary. We have seen a few cases of solitary, large, metastatic tumors in which this procedure has prevented needless surgery.

Exploratory thoracotomy is justified in two groups of patients: (1) those in whom the diagnosis has been established but in whom the operability is questionable, and (2) those in whom primary bronchogenic carcinoma is strongly suspected, but not proved pathologically, and where it is thought wise to proceed without further delay.

Treatment: At the present time, the only known forms of treatment are irradiation, fulguration, and surgical excision. All forms of irradia-

tion to the present time have been failures as curative agents. Graham[4] and his associates have been unable to find any record of a single verified five year cure by this method of treatment. This undoubtedly is due to the high radioresistence in the majority of carcinomas of the lung. Portmann[5] feels that the decrease in the lung shadow which often occurs following irradiation is due to improvement in the obstructed pneumonitis, rather than to an actual decrease in the size of the tumor itself. The lack of clinical improvement from irradiation probably can be explained by the central location of the majority of the tumors.

Intrabronchial insertion of radium for lesions in a stem bronchus has not been eminently helpful and, of course, is practicable only in a very small percentage of cases. Likewise, fulguration has a very limited field, because of the few patients having carcinomatous polyps within reach of the cautery through the bronchoscope.

Since the above procedures are limited in their applicability and will not cure the patient, surgery is the only treatment in the majority of cases. Carcinoma of the lung can be cured by radical surgery if no metastasis or extension to adjacent structure has occurred. Pneumonectomy is the procedure of choice, although a few cases have been reported as cured by lobectomy. One of us (T. E. J.) has a nine year proved cure of bronchogenic carcinoma following lobectomy.

Exploratory thoracotomy is indicated in any case of proved primary carcinoma of the lung without direct clinical evidence of metastasis and also in any case of suspected lung neoplasm. This is true even in spite of roentgen evidence of mediastinal extension, as occasionally the glands will be inflammatory secondary to lung suppuration and not to metastasis. Exploration also is justified even in the presence of a complete atelectasis of the involved lung which may be caused by edema secondary to the bronchial neoplasm or to a pedunculated polyp with malignant degeneration, as will be shown in the case reported.

Pneumonectomy may be indicated even though direct extension to the chest wall has occurred over a small area, or this area of chest wall may be excised. However, this decreases the possibility of a cure as metastasis probably will have occurred through the intercostal lymphatics.

The contraindications to exploratory thoracotomy are (1) obvious clinical metastasis, (2) a neoplasm located at the carina or tracheal wall instead of a main stem bronchus. The presence of Horner's syndrome is usually considered a contraindication, as it signifies mediastinal involvement of the sympathetic chain.

Operations were performed on nine of the thirteen cases in this group of cases. The other four were clinically inoperable or refused surgical intervention. The following table summarizes the operated cases:

TABLE 1

Sex	8 men, 1 woman
Age	Youngest 41, oldest 68, average 52 years
Cough	7 cases
Fever	6 cases
Chest pain	7 cases
Horner's syndrome	2 cases
Tumor suspected by roentgen examination	4 cases
Ulcerating type of carcinoma by roentgen examination	2 cases
Side of lesion	Right, 5 cases, left, 4 cases
Diagnosis confirmed by bronchoscopic biopsy	6 cases
Aspiration needle biopsy	2 cases
Exploratory thoracotomy	1 case
Pneumonectomy	7 cases

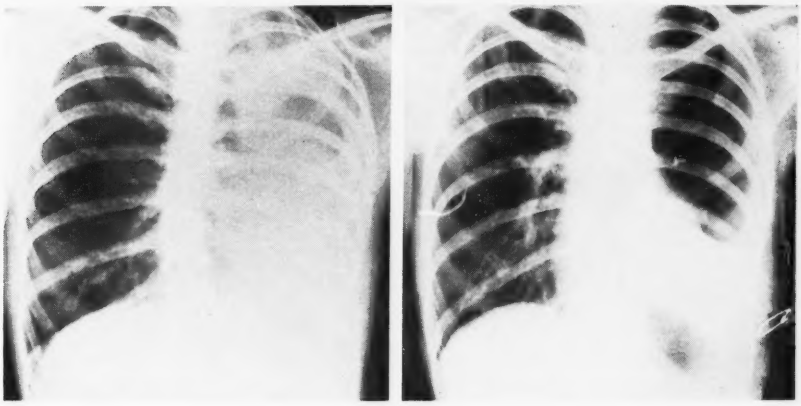
The surgical mortality in this group of cases to date is two out of nine. Although this small group of cases chosen over a short period of time does not warrant many conclusions, the following points are of clinical interest: (1) The youngest patient was forty-one years of age and the oldest sixty-eight, the average age being fifty-two years. (2) Seven of the nine cases had early symptoms of cough; two had never coughed. Six had bouts of fever. Seven had pain in the chest. The two cases with Horner's syndrome were found at exploration to be inoperable for removability of the tumor. (3) Carcinoma of the lung was suspected roentgenographically in only four of the nine cases. The other five were more typical of other entities, such as tuberculosis, bronchiectasis, and so-called "unresolved pneumonia." In two patients the ulceration resembled a tuberculous cavity or lung abscess on the films. (4) The diagnosis was confirmed by bronchoscopic biopsy in six cases, by aspiration needle biopsy in two, and by exploratory thoracotomy in the one remaining case. (5) In seven of the nine cases, pneumonectomy was carried out. One case in this series was most unusual and merits a detailed report as follows:

CASE REPORT

A forty-one year old, married, white woman was admitted to the Clinic on March 27, 1940, complaining of a cough which had been present for two years.

Present History: The patient stated that the present condition started with an attack of influenza in December, 1938. About two weeks later she was taken to the hospital and pus was aspirated from the left chest. She was told that she had tuberculosis and she was placed in a sanatorium for two months. During this time repeated sputum examinations failed to show tubercule bacilli. She stated that the opinions of the doctors as to whether or not she had tuberculosis were divided. Since that time she had continued to cough.

The past history was irrelevant.



A. B.

FIGURE 1: A. Roentgenogram taken on admission, showing complete atelectasis of the left lung.
B. Postoperative roentgenogram showing a moderate degree of empyema (pneumonectomy sixteen days previously).

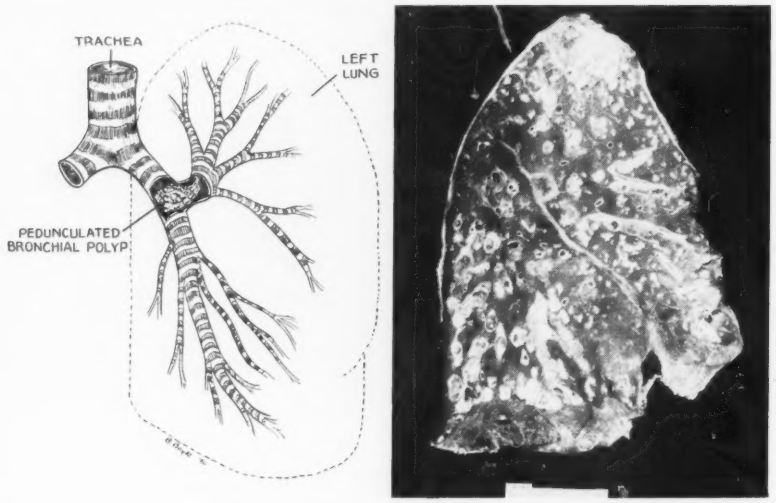
Physical Examination: The temperature was 98.8° F., the pulse 106, and the blood pressure 108 systolic, 75 diastolic. The percussion note over the entire left chest was flat. The breath sounds were vesicular above the seventh dorsal vertebra, but were absent below this level. No râles were heard in the chest.

The physical diagnosis was atelectasis of the left lower lobe, etiology a questionable bronchial neoplasm.

The laboratory examinations were negative except for a mild secondary anemia. A blood count revealed 3,500,000 red cells with 65 per cent hemoglobin. Roentgen examination showed atelectasis of the left lung (Fig. 1 A). Bronchoscopy was performed on April 18, 1940. Protruding into the left main stem bronchus from the region of the upper lobe bronchus was a mass of friable tissue obstructing the lumen. Biopsy was taken and was reported to be squamous cell carcinoma.

Left pneumonectomy was performed on April 24, 1940, and a completely atelectatic lung was found diffusely adherent to the lateral chest wall, pulling the heart and mediastinum into the left chest. An intercostal drainage tube was inserted into the bottom of the pleural space because of contamination. The postoperative course was uneventful until the sixteenth day when a temperature of 101° F. developed. Roentgen examination of the chest showed a fluid level above the intercostal tube (Fig. 1 B). Thoracentesis was done several times, and finally a rib resection was done on May twentieth, twenty-six days after pneumonectomy, revealing a small localized empyema about the tube. Convalescence was uneventful and she was discharged on the thirty-fifth postoperative day.

Pathological Examination: In the left main stem bronchus (Fig. 2 A and B) just proximal to the major branches, was a pedunculated polypoid tumor 1 x 2 cm. protruding up the main stem bronchus. Advanced bronchiectasis of the entire lung was present, secondary to the polypoid obstruction. Microscopic examination revealed a carcinoma simplex originating in the bronchial mucosa. Examination of three mediastinal lymph nodes showed no evidence of metastasis.



A. B.

FIGURE 2: A. Drawing from surgical specimen, showing a pedunculated polyp arising at the point of division of the bronchi of the left upper and lower lobe. This polyp extended centrally into the left main stem bronchus, occluding the drainage of the entire lung.
B. Photograph of an anteroposterior cross section of the left lung demonstrating the advanced bronchiectasis secondary to the obstructing polyp.

This case presents early carcinomatous degeneration of a benign bronchial polyp. The location of the polyp rendered useless all hope of treatment by bronchoscopic approach.

SUMMARY

There apparently is both a relative and an absolute increase in the incidence of primary carcinoma of the lung. Our hope of recognition of early cases rests on close cooperation between the internist and the bronchoscopist, as well as the surgeon.

With our present day knowledge, the only hope of cure is by surgery, either in the form of lobectomy or pneumonectomy.

A group of cases is discussed with reference to surgical approach, with a report of an unusual case.

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UROLOGICAL PRACTICE AND BIOCHEMISTRY

W. E. Lower, M.D. and D. Roy McCullagh, Ph.D.

The marked advances in the medical sciences have been the result of cooperative efforts in the fields of clinical investigation and laboratory research. These achievements have been accomplished largely by tedious investigations which prove fruitless more often than fruitful. In the field of urology alone, in which we are particularly interested, many of the advances have been direct results of investigations in the chemical laboratory. Without any attempt to review the vast literature, some of the more practical results of collaborative efforts between urologists and biochemists will be discussed.

It is not possible here to mention the multitude of biochemical tests for the analyses of blood and urine which are of diagnostic as well as prognostic value in urological practice. Most of these tests are also useful in general medical practice. At present, we will mention only some of those tests which are of special urological interest.

Diodrast has been a very useful chemical in the making of pyelograms. It is nontoxic and its intravenous administration is not followed by any serious reaction. It can readily be used in the making of pyelograms in small children or infants. Under many circumstances when retrograde pyelography is contraindicated, a roentgenogram can be obtained following the intravenous injection of diodrast. When used in making retrograde pyelograms, it is much more satisfactory than sodium iodide because it is less irritating to the delicate mucous membranes of the urinary tract.

Various chemicals have been made which are of tremendous importance in the determination of kidney function. The use of indigocarmine enables the diagnostician to determine quickly individual kidney function when ureteral catheters are in place. The phenolsulphonphthalein test has been used to great advantage in the diagnosis of surgical diseases of the kidney. In patients suffering from nephrosis or one of the nephritides, total kidney function can be determined by the urea clearance test.

In the field of urinary antiseptics, much could be written in regard to recent chemical contributions. At one time, no thought was given to the probability of having specific chemotherapeutic agents. Treatment with sodium acid phosphate and urotropin, which is very valuable, was used in attempting to control any or all types of infection. It is now known that ketogenic diets and mandelic acid are particularly efficacious in combatting the colon bacillus and the streptococcus fecalis. The discovery of the usefulness of the sulfanilamide group has been of the greatest importance to the urologist. The first member of this group

to come into common use was prontosil which was very useful in the treatment of streptococcal infections, as well as in other conditions. Recently, sulfanilamide and sulfapyridine have been widely used in streptococcal and gonococcal infections. Sulfapyridine probably is less toxic than most other available compounds of this type. Very recently, experiences with sulfathiazol indiate that it is probably very efficacious in regard to staphylococcal infections of the urinary tract.

In addition to the production of these antiseptics, the chemist plays a valuable role in controlling their proper therapeutic use. The mode of absorption and excretion has been studied. Quantitative methods for measuring the antiseptics in the blood stream have been developed. The mode of action on the organisms has been investigated. Methods for determining the most satisfactory quantities to administer have been devised.

During the past decade notable advances have been made in regard to our knowledge of urinary lithiasis. The gaps are so great that extensive researches still are necessary. It has long been recognized that infection and stasis are definite predisposing factors in the production of calculi, but it is only within recent years that the very important question of diet has received proper emphasis.

Vitamin A deficiency has been demonstrated to be a major etiological factor in the production of many stones, particularly of the phosphatic type. It is known that this vitamin is of great importance in the maintenance of epithelial structures. It seems that desquamated keratinized epithelium from the urinary tract provides a nucleus about which crystalline depositions readily form. The frequency of renal calculi in vitamin A deficiency has been demonstrated in experimental animals and in man.

For reasons other than vitamin deficiency, the diet is a very important consideration in regard to the formation of stones. By controlling the diet, it usually is possible to control the acidity of the urine over a considerable range of pH. This is very useful as a therapeutic aid because uric acid calculi are much more soluble in alkaline medium whereas phosphatic calculi increase in solubility as the urine becomes more acid.

Improved methods for the analysis of calculi have been developed. This has become a matter of importance because of the fact that many calculi tend to recur. If the nature of the stone is known, the recurrence can be combatted more readily.

By no means has the least of the biochemical contributions in the field of urology been in the investigation of the sex hormones. The literature on the subject is so tremendous that to summarize it briefly is impossible. The investigations of greatest interest to the urologist are

those concerned with testicular disorders. In studying cases of impotence, sterility, or cryptorchidism, it frequently becomes important to know whether or not the condition is of endocrine origin. In addition, it is important to discover whether or not glands other than the testes are involved. In making such a diagnosis, laboratory studies to determine the amount of testicular and gonadotropic hormone being excreted can be of considerable assistance.

The assay for androgens (male sex hormones which directly stimulate male characteristics) can be carried out in numerous ways. No matter what method is employed, it is necessary first to separate the hormone from other urinary constituents. This concentration can readily be affected by the use of fat solvents. The hormone is recovered from the solvent and measured either by biological or by chemical methods. Numerous biological procedures have been used, including the effect of the androgens on the seminal vesicals, the prostate, and the production of semen in experimental animals. By far the most satisfactory biological method for routine clinical use is that based on the measurement of the growth of the comb of the capon after the bird has been treated with the hormone.

In the normal male, sufficient hormone is present in the urine to make it possible to extract it and inject it into capons in order to make this test. In children and in hypogonadal individuals, the amount of androgen present is lower and in order to accomplish a satisfactory assay, it is necessary to increase the sensitivity of the test. This can be done by inuncting the material directly onto the comb instead of injecting it into the capon.

Recently, considerable effort has been made to devise satisfactory chemical methods for measuring androgens in urinary extracts. The androgens which are quantitatively the most significant in normal urine are ketonic in nature and possess a chemical configuration which results in their reaction with meta-dinitrobenzene, to produce a red color. The depth of the color can be used as a measure of the amount of hormone present. Under certain circumstances nonketonic androgens are present in the urine. These cause growth of the capon's comb but do not give the color reaction. In such instances, they can be detected only by biological assay.

When the testes are not producing the normal amount of hormone, the pituitary gland becomes hyperactive. Several laboratory tests for overactivity of the pituitary gland are available. The pituitary sex hormones are known as gonadotropins because they stimulate the gonads. They are extremely complex chemical elements and chemists have not been able to devise a satisfactory chemical method for their detection. However, excellent procedures are available for the separation of these hormones from the urine. When separated, biological determination is

possible. Most methods of bio-assay for gonadotropins are based on the fact that they stimulate the ovaries of experimental animals. The amount of stimulation is a measure of the amount of hormone present.

One of the very greatest chapters in chemistry has been that dealing with the sterols. Some of the adrenal substances, the ovarian hormones, and the androgens are all derivatives of the sterols. The isolation of these substances from their natural sources and the subsequent production of many of them from cholesterol and other sterols have been significant achievements of the chemists. The urologist finds the androgens of especial interest. The androgen which is in most common use therapeutically is testosterone propionate. It has been of very great value in the treatment of testicular deficiency. In addition, numerous reports have appeared in the literature in regard to its efficacy in the treatment of prostatic hypertrophy. However, further clinical research is necessary to determine its value, if any, in this group of cases.

The efforts of biochemists have been successful in the production of hormones for the treatment of certain forms of cryptorchidism and sterility. There is every reason to believe that they can contribute further to the treatment of these diseases. Although some reports would indicate that testosterone and possibly some of the other androgens are injurious to the testes, there is incontrovertible evidence that under certain circumstances the androgens are a very definite aid and a stimulant in the production of sperms. Following hypophysectomy in the rat, the testes become inactive very quickly, both in regard to sperm production and to hormonal function. However, if adequate doses of androgens are administered, normal production of sperms can be maintained for a long period. The proper clinical application of this principle has not yet been developed.

While considering testicular disorders, the fact that the testes produce a non-androgenic hormone known as inhibin seems worthy of mention. This hormone was discovered and has been studied by many investigators, using the rat. It is now known, however, that inhibin is present in bovine testes and is effective in human beings. This hormone was called inhibin because it seemed probable that its most important function was that of depression of the pituitary gland, particularly in regard to its gonadotropic function. In experimental animals, it has been shown that the hyperactivity of the pituitary gland which follows castration can be controlled by the injection of inhibin. When inhibin is injected into normal animals, it causes a decrease in the size of the prostrate gland presumably because of decreased androgenic production by the testes as the result of the lessened pituitary activity caused by inhibin. Because of this experimental finding, inhibin has been used in the treatment of prostatic hypertrophy in humans. Strangely enough, no one has yet been able to demonstrate any changes in the human

prostate gland following treatment with inhibin. There is no question, however, that treatment with inhibin has greatly relieved the urinary retention in many instances. As in other instances of endocrine replacement therapy, the treatment appears to be effecive only as long as medication is continued.

In that inhibin was so effective in the male, its influence on the female was also studied. It acts as a very powerful sexual depressant in experimental animals. Normal female rats which have been observed to have regular sexual cycles every three or four days, as indicated by vaginal smears, can be forced to go into diestrus (the resting stage of the sexual cycle) as long as the injections of potent inhibin preparations are continued. Clinical experiments have been undertaken but reports are not yet available.

Conclusions

In this very brief review in which only a few of the pertinent facts have been mentioned, an attempt has been made to demonstrate how medical science definitely has advanced as a result of the collaboration of two of its branches. A multitude of such examples could be found to prove that no scientific specialty can function to greatest efficiency except by some such method of cooperation.

FOREIGN BODY IN THE ESOPHAGUS

Report of a Case

PAUL M. MOORE, JR., M.D.

A foreign body in the esophagus always causes some disturbance in deglutition. There may be dysphagia or odynphagia. Usually the two are combined and the patient not only is unable to swallow food, but also has definite pain in the process. In addition to this, he usually can indicate the level at which the obstruction exists. The amount of obstruction to the passage of food depends on the size and shape of the foreign body. There usually is a definite history of the onset but in infants and small children this history may be lacking since the object may have been swallowed when the child was alone. There may be no definite pain. The only sign which may be noticed is that the child does not eat well. He may refuse all solid food or may vomit solid food when he attempts to eat it. Reluctance to eat is not an entirely reliable sign because many children pass through a period in which they pick at their food and take a long time and much persuasion to eat a meal. However, when a child who has previously eaten well suddenly begins to refuse food, he should be suspected of having a foreign body in the esophagus. Anteroposterior and lateral roentgenograms should be taken. If a radiopaque foreign body is present, it will show in these films. If these are negative, barium should be given and its progress through the esophagus watched under the fluoroscope. Roentgenograms should be taken of any deviation from normal. These will show the presence of a nonopaque foreign body. If all of these examinations are negative, probably no foreign body is present although a small one still could be caught in a fold in the esophagus, and produce pain. In older people the possibility of an early carcinoma always should be borne in mind. It is well to advise esophagoscopy in all such cases.

A small sharp foreign body may pass through the esophagus and not lodge in it, but in passing may scratch the esophageal mucosa. This leaves the sensation of a foreign body being present and there is pain on swallowing. If roentgen studies are negative, a short period of observation may be followed before esophagoscopy is done. This is not safe, however, unless careful roentgen studies are made. I have seen one case that ended fatally from perforation of the esophagus and aorta by a chicken bone. The family physician had not made roentgen studies and because discomfort diminished, nothing was done until a massive hemorrhage from the esophagus occurred. Only then was the patient referred to the hospital for study.

CASE REPORT

The following case is reported because it illustrates the importance of a careful and thorough investigation in every child who presents any symptom which might

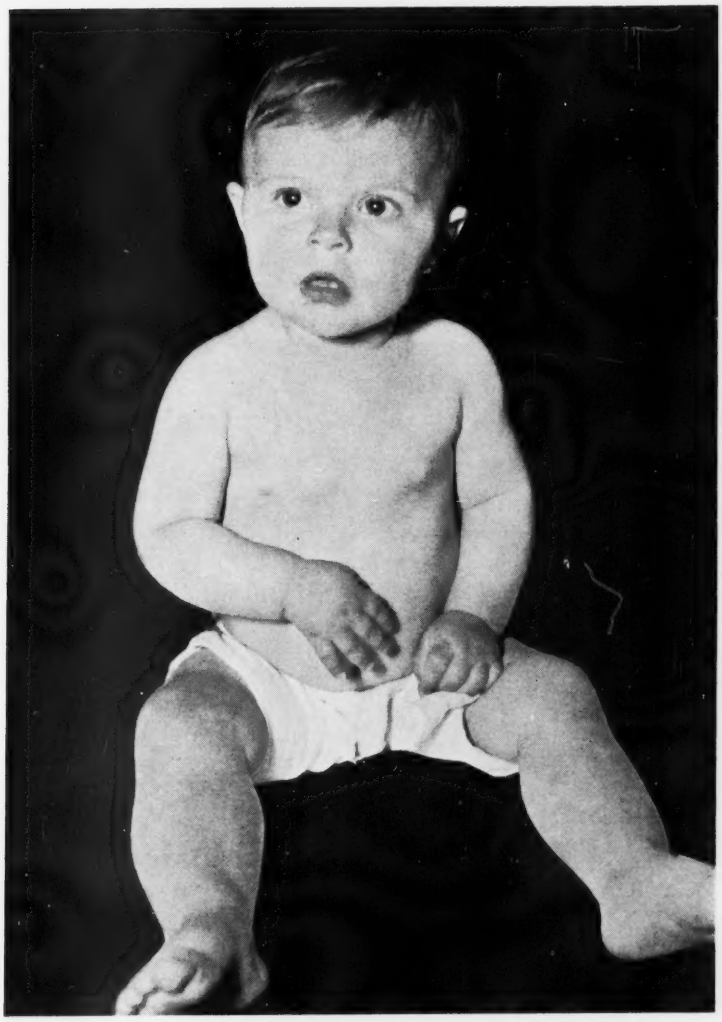


FIGURE 1: Photograph showing excellent condition of the patient even though she had subsisted on a liquid diet for almost a year.

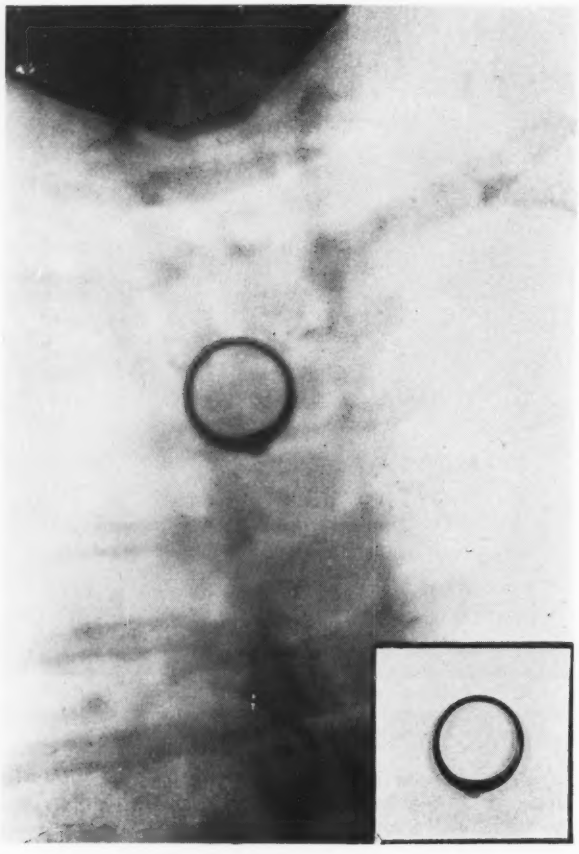
be caused by a foreign body in the food or air passages. It also is of interest because of the remarkably excellent condition of the patient in spite of her inability to swallow anything but liquids for almost a year.

The patient, a white girl fifteen months of age, was admitted to the Cleveland Clinic Hospital on July 16, 1940, with the complaint of inability to swallow solid food since the age of four months. She vomited whenever she attempted to eat any solid food and had subsisted entirely on a liquid diet during this time. In

spite of this handicap, she was in excellent health, had gained weight steadily, and had no illnesses of any kind. Fluoroscopic examination, done that day by the referring doctor, revealed a ring in the upper end of the esophagus.

Examination showed a well nourished, active and healthy infant (Fig. 1). The nasal passages were clean and clear, the tonsils were small and submerged, and there was no inflammation in the pharynx. The external auditory canals contained a small amount of cerumen. Both drums were of good lustre and transparency. The chest showed good and equal expansion. The lungs produced normal resonance and breath sounds throughout. The heart was not enlarged, and the heart sounds were normal.

Roentgen examination showed a metal ring with a setting just above the level of the aorta. The broad axis of the ring was at right angles to the sagittal plane (Fig 2 A).



A. B.

FIGURE 2: A. Roentgenogram showing ring just above the level of the aorta.
B. Photograph of the black, tarnished, gold ring removed from the esophagus of this patient.

A Hasslinger 8.5 mm. esophagoscope was passed easily without anesthesia. A black foreign body was visualized just above the level of the aortic arch. Although there was no evidence of inflammation of the mucosa, the esophagoscope met with definite resistance, preventing its reaching the foreign body. This suggested that some inflammation in the past may have produced scar tissue in the esophageal wall. As the end of the esophagoscope approached the ring, a fold of mucosa rolled up on the posterior wall to hide the ring from view. The esophagoscope then was withdrawn until the ring could be seen again. When the esophageal wall was pulled away during inspiration, the ring was grasped with a ring rotation forceps. A steady straight pull released the ring which was of black tarnished gold with a small blue stone setting (Fig. 2 B).

By evening, she was drinking freely. She also was eating crackers which she had been unable to swallow previously. There was no postoperative reaction. When last seen, she still was timid about eating bread and other solid food, but was taking a soft diet without any difficulty. A barium esophagram subsequent to the removal of the ring showed no evidence of stricture. The child is anatomically capable of swallowing solid foods but is not yet psychologically prepared to accept them.

MANAGEMENT OF URINARY TRACT INFECTIONS

CHARLES C. HIGGINS, M.D.

In recent years, pronounced progress in the management of urinary tract infections has been made primarily because of three factors:

1. A more complete investigation of the urinary tract to rule out the presence of coexisting pathological conditions. The ease with which this may be accomplished has been facilitated greatly since the introduction of intravenous urography.

2. A thorough bacteriological study, including a stained smear of the sediment and such cultural investigations as are deemed necessary to classify the organism. In certain instances, additional cultural studies should be made to determine certain properties which may be possessed by the various organisms, such as the power of splitting urea.

3. The introduction of the newer chemotherapeutic agents. Since sulfanilamide and mandelic acid have been made available, numerous drugs which have been employed in the treatment of urinary tract infections in the past have been discarded and the management of such infections has been placed on a strictly scientific basis.

Although the type of organism present definitely influences the choice of drug to be prescribed, additional conditions merit consideration before mandelic acid or sulfanilamide are used. In the aged, the blood urea and carbon dioxide should be studied frequently as acidosis may result from the administration of mandelic acid. The use of sulfanilamide may produce a similar result, but with the simultaneous administration of sodium bicarbonate, it occurs to a lesser degree.

With impairment of renal function, further depression of function may follow the use of either drug, and concentration of the drugs in the urine may not be sufficient to exert bacteriocidal effects. Lack of tolerance or an idiosyncrasy to either of the drugs may prevent its use for the time needed to secure satisfactory results.

Occasionally, recurrent infections of the bladder in men fail to respond to the use of mandelic acid, usually because a persistent infection in the prostate and seminal vesicles continues to reinfect the bladder. In such cases, sulfanilamide is prescribed for its bacteriostatic action.

Mandelic acid therapy may be utilized when Escherichia coli, Aerobacter aerogenes, and Streptococcus fecalis are isolated from the urine. Members of the genera Salmonella, Pseudomonas, and Shegella may respond to this therapy. The ammonium salt in the elixir form, containing approximately 28 per cent of the salt, is usually administered in three fluid drachms (12 cc.) after meals and at bedtime. Approximately 12 gm. of the pure acid are required a day for satisfactory results.

Certain conditions must exist in order to eradicate the infection: (1) The pH of the urine must be maintained between 5.3 and 5.5, (2) the concentration of the drug in the urine must be between 0.9 and 1.0 per cent, and (3) the fluid intake must be restricted to between 1,000 and 1,200 cc. a day.

If mandelic acid alone does not maintain the pH of the urine at the desired level, acidifying agents such as ammonium chloride or ammonium nitrate may be prescribed. As mandelic acid is eliminated almost entirely in the urine, the concentration of the drug in the urine may be determined readily from the output of urine in a twenty-four hour period, and the amount of the drug taken daily. The medication may be continued over a period of ten days to two weeks unless a toxic reaction or an idiosyncrasy to the drug is evident. If after an interval of a week or ten days the culture of the urine is positive, a second course of treatment is indicated. Mandelic acid therapy will be efficacious in eradicating approximately 85 to 90 per cent of uncomplicated infections of the kidney and bladder.

Sulfanilamide may be used when the organisms are Escherichia coli and Aerobacter aerogenes. It also exerts a bacteriocidal effect in alkaline urine, and thus has a distinct advantage over mandelic acid which acts efficaciously only in the presence of strongly acid urine. Sulfanilamide, therefore, may be used in the presence of urea splitting organisms which form ammonia and render the urine strongly alkaline. Accordingly, certain cases of uncomplicated infections caused by the proteus organism may respond to this medication. However, in the coccal group of infections, our results from the use of sulfanilamide have not been striking.

The prescribed dosage of sulfanilamide varies with the authors advocating this drug. In treating urinary tract infections in adults, I prefer the following dosage: 60 gr. (4 gm.) a day for a period of three days, to be taken after each meal and at bedtime; for the next two days a total dosage of 40 gr. (2.65 gm.) if given. After this period, a maintenance dosage of 30 to 40 gr. (2.0 gm.-2.65 gm.) a day for a total period of ten to fourteen days is prescribed. In infants, 5 to 10 gr. are given daily; in children from two to five years of age, 15 gr. daily; from five to ten years of age, 15 to 20 gr. daily; and over fifteen years of age to young adults, 20 to 25 gr. daily.

Equal doses of sodium bicarbonate are given with the sulfanilamide. There is some indication that better results are secured when the drug is administered at regular intervals both day and night. By doing so, it is possible to maintain in the blood a constant free sulfanilamide level of approximately 9 to 10 mg. per 100 cc.

Neoprontosil, which forms sulfanilamide in the body by a process of reduction, also may be prescribed. As has been indicated by other

authors, neoprontosil apparently has a more pronounced therapeutic effect in some instances than can be explained by its sulfanilamide content, and may be employed when the patient does not tolerate sulfanilamide. Forty to 60 gr. (2.65 to 4 gm.) may be given daily.

If sulfanilamide or neoprontosil cannot be administered by mouth because of nausea and vomiting, subcutaneous or intramuscular injections of prontosil are advisable. In an adult, 2 cc. of a 2.5 per cent solution of neoprontosil per pound of body weight to 110 or 120 pounds may be administered daily, one-sixth of the calculated dose being injected every four hours. Careful check of the sulfanilamide content of the blood and repeated blood studies always should accompany the administration of sulfanilamide, and with the appearance of idiosyncrasies or toxic manifestations, the use of the drug should be discontinued.

Neoarsphenamine is an extremely useful drug in the presence of coccal infections and eliminates the cocci from the urine in from 40 to 50 per cent of uncomplicated cases. In many instances, however, it does not render the urine sterile.

Sulfathiazol and sulfamethylthiazol* in which the thiazol radical has been substituted for a hydrogen radical in sulfanilamide have been produced recently. Insufficient time has elapsed in my experience for me to make definite statements regarding these drugs.

With the introduction of any new medication, the possibility of complications should be kept in mind, and overenthusiasm about results secured in a small series of cases should be avoided. Pool and Cook[1] in citing a series of fifty patients treated with these drugs state that, in their opinion, these two new derivatives of sulfanilamide are less toxic than either sulfanilamide or sulfapyridine.

Of five patients, in whom Staphylococcus aureus was isolated in the urinary tract, four received sulfamethylthiazol and one, sulfathiazol. The urine in all these patients became sterile and remained so. The dosage of both these drugs is usually 15 gr. (1 gm.) four times a day.

Although sulfapyridine may be used to combat infections of the urinary tract, it appears to be no more efficacious for eradicating the infection than sulfanilamide. Signs of renal irritation may accompany its use over the period of time needed to eliminate the organisms from the urine, and renal calculi may be produced. Moreover, the cost of the drug is almost prohibitory to the majority of patients.

In patients in whom a mixed infection is present, successful eradication of the infection in the uncomplicated case depends upon a careful bacteriologic study. One or more drugs may be necessary to render the urine sterile. This is especially true in the presence of chronic pyelonephritis in which a mixed infection is present in over 10 to 12 per cent of

*Since the writing of this article, sulfamethylthiazol has been withdrawn from the market.

cases. When colon bacilli and staphylococcus are coexistent, mandelic acid may be utilized to eliminate the bacilli from the urine and sulfanilamide or neoarsphenamine to eradicate the coccal infection.

Today, the majority of uncomplicated infections of the urinary tract can be eradicated by a scientific approach to the problem. Incomplete bacteriologic studies will be attended by persistence of the renal infection, which will continue to exert a deleterious effect upon the renal parenchyma, accompanied by impairment of renal function and perhaps even death attributed to renal disease.

Reference

1. Pool, T. L. and Cook, E. N.: Sulfathiazol and sulfamethylthiazol in the treatment of infections of the urinary tract, Proc. Staff Meet. Mayo Clin., 15:113-116, (February 21) 1940.

THROMBOSIS OF THE PULMONARY ARTERIES

Report of a Case

H. O. SCHNEIDER, M.D. and H. SCOTT VAN ORDSTRAND, M.D.

Circulatory failure of an extracardiac nature caused by pulmonary emphysema, kyphoscoliosis, sclerosis of the pulmonary arterioles, and Ayerza's disease is not too uncommon to warrant intensive clinical investigation. The classical syndrome of dyspnea, cyanosis, pain in the chest with or without cardiac signs, and a normal blood count may tax the acumen of the clinician to differentiate between pulmonary or heart disease. A patient who recently entered the Cleveland Clinic presented this syndrome.

CASE REPORT

A forty-seven year old white woman entered the Clinic on April 29, 1940, with the complaint of cough, pain in the chest, loss of weight, nervousness, fever, and shortness of breath. The patient dated the onset of her illness to a difficult labor four years previously. Her only symptom was dyspnea on moderate exertion until September, 1939, when she began to have nervousness, palpitation, and increasing dyspnea on lessened exertion. Two months later, the patient noticed "knots" on the abdomen which were not sensitive to touch, and swelling of the veins on the posterior aspect of the thighs and over each buttock. Associated symptoms were loss of weight and swelling of the ankles. The basal metabolic rate taken at that time was plus 40 per cent. Roentgen examination of the chest was normal. Her symptoms were not alleviated by the use of digitalis, Lugol's solution, and bed rest, but they improved spontaneously, and she was quite active for four months.

Four weeks before examination at the Clinic, the patient began to cough, producing about one cup of sputum daily which recently became pink-stained and foamy, but did not contain gross blood. Two weeks later, fever developed, and she complained of a dull pain over the right side of the chest anteriorly and posteriorly, which was not related to respiration. The patient had noticed increased perspiration and had been told that she had a heart murmur and a fast pulse. The menses had been scanty during the previous six months.

Physical examination revealed a well-developed woman who weighed 120 pounds, representing a loss of sixty pounds during the previous eight months. She was acutely ill and apprehensive. The eyes had a glassy appearance. Cyanosis of the lips and nail beds, and ptosis of the eyelids were present. The skin was soft, velvety, and moist. The thyroid was palpable. The lungs were normal throughout, except for bronchophony and whispering pectoriloquy with numerous moist râles in a small area in the right infraclavicular space. Examination of the heart revealed a rate of 120 beats per minute and gallop rhythm. The area of cardiac dullness extended 11 cm. to the left of the midsternal line in the fifth interspace. All sounds were forceful. There was a moderate systolic and a rumbling diastolic murmur at the apex. A moderate systolic murmur was heard over the base, being louder over the aortic area; A_2 was greater than P_2. A mitral flush was present.

The veins over the abdomen were distended and filled from below. The liver was firm and nontender and extended three fingers breadth below the right costal margin. The spleen was not palpable. There was moderate edema of both legs and a fine tremor of the hands.

On admission, the diagnosis was: (1) Nodular goiter with possible hyperthyroidism, (2) rheumatic heart disease with mitral stenosis and insufficiency, (3) pulmonary tuberculosis, and (4) cirrhosis of the liver.

Laboratory studies revealed a normal urine except for a trace of albumin. Blood studies revealed 4,180,000 red cells with marked central pallor, 75 per cent hemoglobin, and 14,600 white cells (of which 96 per cent were neutrophils, 2 per cent lymphocytes, and 2 per cent monocytes). The icterus index was 4, and the platelets numbered 280,000. The coagulation time, bleeding time, clot retraction, and prothrombin time were normal. The sedimentation rate was moderately elevated, the blood sugar while fasting was 91 mg. per 100 cc., and the blood cholesterol was 83. Wassermann and Kahn tests of the blood gave negative reactions. Examination of the stool was negative. Sputum examinations were negative for tubercle bacilli and spirochetes. The bromsulphalein liver function test showed 32 per cent retention of the dye after thirty minutes. Gastric aspirations for tubercle bacilli were negative. The basal metabolic rate was plus 68 per cent.

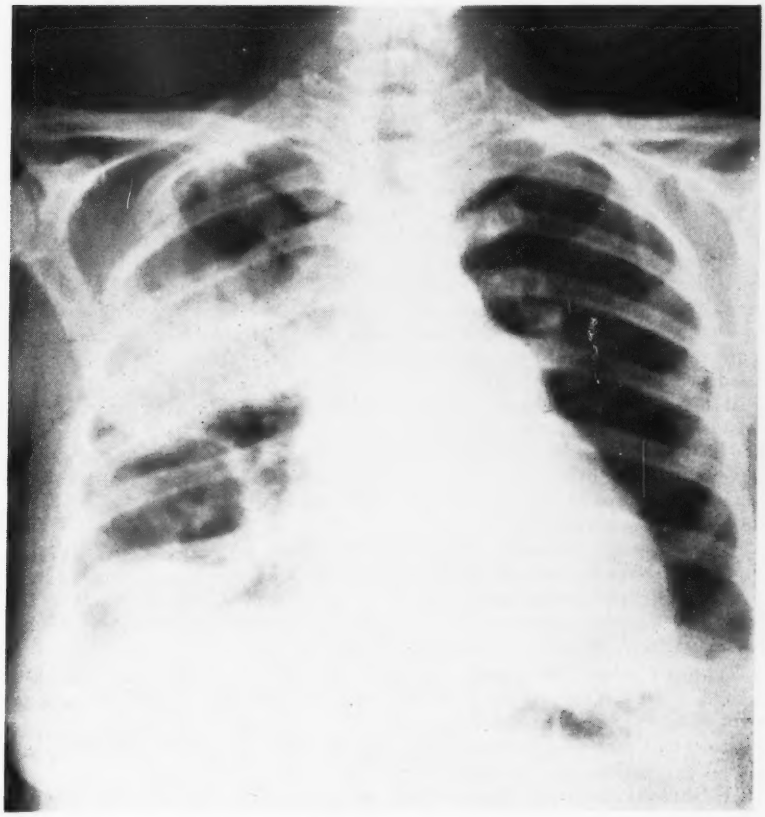


FIGURE 1: Roentgenogram of the chest showing large cavities in the right lung. These proved to be abscesses caused by ischemic necrosis.

Roentgen examination of the chest (Fig. 1) revealed an enlarged heart, an inflammatory process with cavitation in the upper right lung, partial pneumothorax on the right side, and a large cavity containing fluid in the lower lobe of the right lung. The mediastinum was obscured.

On admission to the hospital, the temperature was 101.3° F., the pulse rate 120, and respirations 26 per minute. On the third day, roentgen therapy was administered to the region of the thyroid gland, 200 r being given at that time. Two additional treatments of 200 r each were given, making the total dose 600 r. The temperature returned to normal following the first administration of roentgen therapy.

The first strength tuberculin test (purified protein derivative) was negative, but the second strength tuberculin (P. P. D.) was strongly positive. On May 7, 1940, the seventh day in the hospital, numerous petechiae appeared on both legs and the abdomen. Special blood studies revealed no evidence of blood dyscrasia. On this day, the patient became more dyspneic, acutely cyanotic, and suddenly expired.

Necropsy revealed that the right lobe of the liver was grossly enlarged and extended to the level of the iliac crest. The left lobe of the liver was absent. The remaining abdominal organs occupied their normal positions and were not grossly enlarged. The abdominal cavity contained no free fluid.

The iliac veins were thin, fibrous cords and were densely adherent to the surrounding structures, apparently from an old phlebitis. Section showed the veins to be occluded up to the inferior vena cava. Canalization was evident, particularly on the left side.

The right pleural cavity contained about 200 cc. of turbid, yellow fluid lying in its lower lateral part. Most of the right lung was adherent to the chest wall. On removing it, a part of the lower lateral wall was torn, revealing a large cavity in the lower lobe. Except for a thin shell of pleura and underlying tissue, almost the entire upper quarter of the lung was absent. At the lower limit was an irregular necrotic wall of an abscess cavity. In the anterior part of the lower lobe was a grossly irregular abscessed cavity which also involved the greater part of the middle lobe. It measured 6 x 6 x 4.5 cm., contained little pus, and consisted primarily of necrotic tissue.

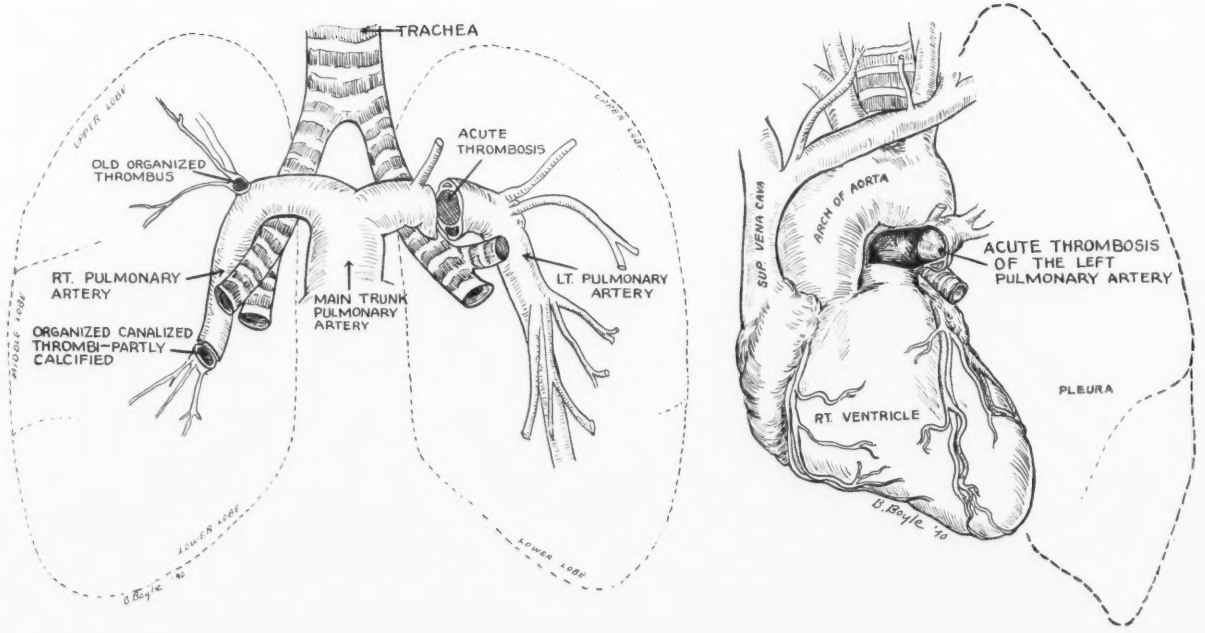
At the entrance to the branch of the pulmonary artery supplying the upper lobe, a moderately large, partly calcified thrombus measuring 1.5 x 0.8 cm. was firmly attached to the wall of the vessel, completely occluding it. There was marked narrowing of the branches of the pulmonary artery which supplied the anterior portion of the lower lobe. The cavities in areas supplied by these vessels resulted from ischemic necrosis.

In the left lung, there were no infarcts or gross pneumonic areas. Throughout the lower lobe were areas of partial atelectasis, congestion, and edema. In the branch of the pulmonary artery which led to the lower lobe there was a large organized thrombus measuring 3 x 1.5 cm. which almost completely occluded the vessel (Fig. 2 A and B). The upper lobe was normal.

The heart weight 350 grams. The right auricle and ventricle were markedly dilated. The left side of the heart was normal. The appearance and measurement of the valves were normal.

Gross and microscopical section of the liver showed well-advanced, diffuse, fatty degeneration.

The thyroid gland was finely lobulated and showed some increase in colloid. The right lobe weighed 28 grams and the left lobe, 15 grams. Some small adenomas were present on the upper pole of the right lobe. Sections from both lobes showed slight hyperplasia.



A. B.

FIGURE 2: A. Drawing of pulmonary arterial supply from necropsy specimen. Note the partial obliteration of the peripheral arteries on the right side from old thrombi occluding the branches to the anterior part of the upper lobe and anterior portion of the lower lobe.

B. Necropsy finding of the secondary, acute, almost complete, occlusion of the left pulmonary artery.

Discussion

Sclerosis of the pulmonary arterioles, and the pulmonary artery with or without general arteriosclerosis is not uncommon. Montgomery[1] described a case of thrombosis of the pulmonary artery similar to the case presented above. In his case, the patient died of circulatory failure. At necropsy the essential lesions were thrombi obstructing the branches of the pulmonary artery. The following explanation for the etiology of the thrombi was given: "It is conceivable that the thrombus in the left main branch of the pulmonary artery had resulted from partial organization of an embolus arrested here after parturition eight years ago, for according to the history the patient had never been completely well since that time." This corresponds with our case, as our patient dated the onset of her symptoms to a difficult labor four years previously. In Montgomery's case, there were 4,500,000 red cells with 60 per cent hemoglobin and 16,000 white cells. As all cases he reviewed developed extreme hypertrophy of the right ventricle, he concluded: "Pulmonary artery obstruction whether of the larger or smaller branches induces a hypertrophy of the right ventricle greatly in excess of that ordinarily produced by long standing mitral disease." Characteristic findings in thrombosis of the pulmonary arteries are: cyanosis and dyspnea, erythrocytosis in long standing disease, a high percentage of hemoglobin, and a color index less than 1.

No case similar to ours with regard to the presence of hypermetabolism could be found in the literature. The pathological condition in the liver might be explained by the obliteration of the iliac vessels. The rare condition of obliterating arteritis may lead to pulmonary infarction. Rothschild and Goldbloom[2] described a case of obliterating arteritis of the smaller pulmonary arteries in which on two occasions there was an elevation of the basal metabolic rate to plus 27 and plus 37. In their patient, the thyroid gland was not palpable, but the thyrotoxicosis was suggested when the patient was first examined. Hence, the surgeon is confronted not only with the differential problem of circulatory failure because of the cyanosis and dyspnea, but also with the problem of possible thyrotoxicosis because of the elevated metabolic rate. However, these authors believed that thyrotoxicosis was not likely since the blood volume, circulatory time, and cardiac output were not increased as they usually are in thyrotoxicosis.

Brenner[3], who has made an intensive study of the pulmonary circulation, does not mention an elevation of the basal metabolic rate in pulmonary artery thrombosis. In his estimation, it is difficult to determine whether or not symptoms of cyanosis, dyspnea, hemoptysis, and pain are due to pulmonary thrombosis or to underlying heart disease. He points out that the patient does not die with this disease until 86 per cent of the vessels have been occluded. This accounts for the relative period of

chronicity of the disease. He also stated that the condition is rarely diagnosed during life because the symptoms are those of ordinary congestive failure. Brenner found many reported cases of thrombosis of the pulmonary arteries, but few cases in which both were occluded. In these cases, the occlusion was completed by an acute thrombosis superimposed on a chronic one. Sudden death was accompanied by pain in the chest, dyspnea, and increasing cyanosis caused by sudden thrombosis of the remaining unoccluded vessels.

Summary

1. A case with the symptoms and signs of circulatory failure and definite cardiac findings has been presented. However, other findings were superimposed upon the cardiac findings to make a diagnosis of heart disease questionable. Clinical and laboratory studies showed evidence suggestive of hyperthyroidism, pulmonary pathology and cirrhosis of the liver.

2. Necropsy findings of obliterated iliac vessels producing a peripheral edema, thrombosis of the pulmonary arteries with subsequent pulmonary infarctions, necrosis, and ultimate cavitation placed the diagnosis in an entirely different category. The enlargement of the right side of the heart was caused by the thrombosis of the pulmonary vessels.

The degree of thyroid hyperplasia did not seem sufficient to produce the marked elevation in the basal metabolic rate. The enlargement of the liver probably was caused by the disturbance of the iliac circulation. The absence of the left lobe would account for hypertrophy of the remaining lobe. There was no evidence of cirrhosis of the liver at necropsy.

3. We were unable to find a parallel case in the literature. Montgomery's case was similar to the one presented, but evidence of an increased metabolic rate, pulmonary cavitation, or enlargement of the liver was not mentioned. The case presented by Rothschild and Goldbloom was one of obliterating arteritis of the smaller pulmonary vessels with the same clinical picture as our case and the one presented by Montgomery, but with an increased metabolic rate of plus 27 per cent and plus 37 per cent on two occasions.

Conclusions

Thrombosis of the pulmonary arteries is rarely diagnosed before death because the symptoms and signs are those of ordinary congestive failure. The condition is not too uncommon to warrant consideration in all cases presenting cyanosis and dyspnea in the presence or absence of cardiac findings or erythrocytosis.

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THE ASSOCIATION OF UNILATERAL KIDNEY DISEASE WITH HYPERTENSION

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That essential hypertension may be associated with and produced by unilateral renal disease seems now to be an established fact, both experimentally and clinically. Equally certain is the fact that not all cases of essential hypertension are due to unilateral kidney disease and conversely that all patients with unilateral renal disease do not have hypertension. We therefore find ourselves in that confusing stage of clinical investigation where we are attempting to determine which case of hypertension can be attributed to unilateral renal disease.

It has long been known that hypertension may be associated with obstructive lesions of the urinary tract or any other disease which results in severe damage and destruction of renal parenchyma, such as in polycystic kidneys. The conception, however, that unilateral kidney disease might produce hypertension is very recent and a large share of credit for stimulating clinical interest in this phase of hypertension must go to the experimental work of Goldblatt[1]. Working with dogs and monkeys, he showed that when the renal artery on one side was constricted with an especially devised clamp, hypertension resulted which usually tended to return to normal after a period of time, although in some instances of unilateral constriction of the renal artery hypertension has been reported to exist for as long as two years. Removal of this ischemic kidney resulted in prompt return of the blood pressure to normal. Goldblatt also showed that constriction of both renal arteries resulted in a sustained elevation of both the systolic and diastolic pressures of the blood. The same results were obtained with constriction of one artery, followed by removal of the opposite kidney. Hypertension in such experimental animals occurs without detectable diminution in renal function, illustrating the difficulty in detecting these cases clinically with the renal function tests employed at the present.

That the renal ischemia produced is responsible for the elevation in blood pressure is indicated by the following facts:

1. If the ischemic kidney is removed, the blood pressure promptly returns to normal; likewise, if the clamp on the artery is removed, the blood pressure falls.

2. If a kidney is transplanted to the neck or groin, as done by Blalock and Levy[2] and Glenn, Child, and Heuer[3], and then rendered ischemic by arterial compression, high blood pressure still results.

3. Further confirmatory evidence was reported by Houssay and Fasciolo[4] who transplanted an ischemic kidney into a normal animal with resultant elevation in blood presure.

It is thus shown that the ischemic kidney is responsible for the hypertension and must be present for it to occur.

According to Goldblatt, the mechanism of the production of hypertension with renal ischemia can be explained in two possible ways only: (1) nervous reflex affecting the general vasomotor apparatus, or (2) a humoral mechanism which postulates the formation of some pressor substance in the kidney which gets into the circulation. By a variety of experiments, Goldblatt[1], Page[5], and others definitely disproved the nervous reflex mechanism by denervation of the kidneys, section of the splanchnic nerve, excision of the entire sympathetic nervous system, etc. None of these procedures prevented the development of hypertension in renal ischemia or relieved it, once produced. The humoral mechanism has been postulated and is indicated by the fact that the removal of the ischemic kidney results in a fall in blood pressure. If the renal vein is obstructed, no elevation of blood pressure results, thus establishing the fact that some substance apparently must get into the general circulation from the kidney. It has been shown that this pressor substance is not excreted in the urine.

An additional method for the experimental production of hypertension is that of Page[5] who showed that wrapping the kidney of experimental animals in cellophane caused an elevation of the blood pressure. At necropsy, the kidneys in these animals were found to be surrounded by a dense hull of tissue 4 to 5 mm. in thickness. Wrapping the kidneys with rubber did not produce such hypertension.

Other important experimental work is that of Hartwich[6], and Harrison, Mason, Resnik, and Rainey[7], who produced hypertension by experimental obstruction of the ureter. Blalock and Levy[2] ligated and divided the ureter to one kidney and showed a moderate elevation of the blood pressure which returned to normal following removal of that kidney. Experimental obstruction of the ureter has thus been shown to produce hypertension.

Thus, we have the experimental proof of the renal origin of hypertension and evidence that unilateral renal disease may produce it. The clinical counterpart to this experimental evidence has recently been forthcoming, with the reporting of a number of cases of hypertension associated with unilateral kidney disease. These cases may be divided into two groups: Group I—those which might be termed the typical Goldblatt kidneys, and Group II—those in which the mechanism is not so clear but probably is due to renal ischemia produced in a different manner.

In Group I may be placed the case of Leadbetter and Burkland[8], in which a rather severe hypertension existed in a child five and a half years of age who had an ectopic pelvic kidney which was removed.

Examination of the specimen showed that the renal artery was partially occluded by a plug of smooth muscle. In the case of Freeman and Hartley[9], a severe type of hypertension developed in a patient who had a single remaining kidney, the other having been removed by nephrectomy several years previously. At necropsy the lumen of the renal artery was found to be markedly constricted by an atheromatous plaque. Hyman[10] reported a similar case in which marked atherosclerosis constricted the lumen of the renal artery. The blood pressure returned to normal following nephrectomy.

In Group II are placed the cases associated with chronic pyelonephritis, hydronephrosis, calculous disease of the kidney, and trauma. According to Bell and Pederson[11], no case of hypertension with chronic pyelonephritis had been reported previous to 1930. Since that time a number of reports have appeared. Longcope and Winkenwerder[12] reported hypertension associated with bilateral pyelonephritis. Butler[13] reported fifteen cases of hypertension associated with chronic pyelonephritis in children, six of which were reported in detail. Of these, two had unilateral pyelonephritis, one being associated with ureteral stone. Nephrectomy was followed by a return of the blood pressure to normal. The case of Barker and Walters[14] is of interest in that there was a long antecedent history of kidney trouble with previous operation for the removal of a stone. Hypertension finally developed and was relieved by nephrectomy. Boyd and Lewis[15] reported a case which was found accidentally at the time of bilateral adrenal exploration, the kidney presenting rather marked infarction. Removal of this infarcted, pyelonephritic kidney resulted in a return of the blood pressure to normal levels. McIntyre[16] also reported a case of unilateral pyelonephritis with hypertension in which removal of the kidney resulted in a return of the blood pressure to normal.

Crabtree[17], in 1938, collected from the literature five cases of unilateral pyelonephritis with hypertension, to which he added one case. In this group, nephrectomy was followed by a return of the blood pressure to normal in four cases. Among these were the two cases previously reported by Butler, and the case of Barker and Walters.

The mechanism of the production of hypertension in these cases is not clear although Crabtree and Prien[18], in a recent study, showed rather marked vascular changes in cases of chronic pyelonephritis. He studied a surgically removed kidney with a rather acute bacillary pyelonephritis. Definite evidence of vascular injury was seen throughout this kidney and where the inflammation was most severe, he was able to demonstrate actual severance of arteries, surrounded by a zone of hemorrhage. In other areas there was involvement of the smaller arteries with intimal damage, lesions which he felt might later lead to occlusion. He called attention to the fact that since the arteries to the kidney are largely

terminal, such injury might produce severe renal damage by ischemia. In considering the mechanism, it has been shown that extracts of pyelonephritic kidneys, as well as other kidneys with ischemia or from patients who had hypertension, have a greater pressor effect than extracts of normal kidney.

Some time ago we became interested in this question and through the cooperation of the medical department complete urological investigation was carried out in cases of hypertension. The seventy-three cases reported here constitute the first group studied and include those seen up to January 1, 1940. This group does not include all cases of hypertension seen at the Clinic during the period of this study, but includes cases which were selected to the following extent.

In general, it consisted of the younger patients. With few exceptions, no case with severe renal insufficiency or evidence of congestive heart failure, or those having had cerebral vascular accidents were referred for urologic investigation because of the belief that they constituted the type of patient whose disease had progressed beyond the hope of relief. In other words, investigation was carried out chiefly in those cases with earlier hypertension where there was some hope of finding a remediable cause. There was, however, no selection of cases on the basis of suspected urologic disease. With the exceptions noted above, they were average cases of essential hypertension. Complete urological investigation was carried out, which included cystoscopy, ureteral catheterization, and careful examination and culture of separate kidney urines, differential phenolsulphonphthalein test and bilateral retrograde pyelography. Also, in many cases, intravenous urography was done and most cases had, in addition, a urea clearance test of kidney function. The ages and sex of the seventy-three cases are shown in Table 1.

TABLE 1

AGE AND SEX OF 73 CASES OF HYPERTENSION

Age		
10-19	2	
20-29	7	
30-39	21	
40-49	21	
50-59	18	
60-69	4	
Total	73	Cases
Sex		
Men	30	
Women	43	
Total	73	Cases

Of the seventy-three patients, ten, or 13.7 per cent were found to have outspoken and severe unilateral kidney disease, and they are summarized in Table 2. Nephrectomy was done in seven of these and we were interested in observing what effect this had upon the blood pressure. We found a significant reduction in four cases, and while two of these later experienced some elevation of blood pressures, they did not return to their original levels. In three cases there was no change in the blood pressure following nephrectomy.

TABLE 2

SUMMARY OF TEN CASES WITH SEVERE UNILATERAL KIDNEY DISEASE

Ureteral stone with obstruction and nonfunctioning kidney	2
Pronounced hydronephrosis with infection	3
Calculous pyonephrosis	3
Pyelonephritis	2

The ages of the four patients in whom improvement was noted were twenty-two, forty-five, forty-eight, and fifty-four years, three having calculous pyonephrosis and the other having an infected hydronephrosis. The three unimproved cases were forty-three, forty-nine, and seventy-three years of age, infected hydronephrosis being present in two while the third had a chronic pyelonephritis associated with a cortical abscess of the kidney. In addition to these ten patients, there were twenty-four others in whom unilateral kidney disease could not be excluded, either because of a definite history, abnormal findings in the pyelogram, functional studies, or urine examinations. Together, there were thirty-four cases, or 46.5 per cent, in whom unilateral kidney disease may have been a factor in the production of hypertension (Table 3).

TABLE 3

UROLOGIC INVESTIGATION OF 73 CASES OF HYPERTENSION

Kidneys normal			39
Severe unilateral kidney disease		10	
Positive history of urinary disease	11		
Duplex kidneys (unilateral)	5		
Chronic pyelonephritis	4		
Previous operation on one kidney	2		
Renal trauma (rupture)	2		
		24	
Total cases with urologic disease			34 (46.5%)

It is granted, of course, that the twenty-four cases referred to may be of doubtful significance, but they were included to record facts which were too outstanding to ignore. For example, there was a definite

history of urinary disease in eleven cases as shown in Table 4, from which it is seen that four had renal colic with passage of stone, two had periodic hematuria of undetermined origin, two gave a history of recurrent pyelitis or persistent pyuria, two had had transurethral resection for prostatic hypertrophy, and one gave a history of bladder trouble of fifteen years' duration, and was found to have a moderate hydronephrosis of the right kidney.

TABLE 4

SUMMARY OF 11 CASES WITH POSITIVE HISTORY OF URINARY DISEASE

Renal colic with passage of stone	4
Periodic hematuria without demonstrable cause	2
Pyelitis, or persistent pyuria	2
Previous prostatic operations	2
"Bladder trouble" 15 years with mild hydronephritis, right	1

There were five patients with a duplex kidney, two of which had complete ureteral reduplication. The significance of these cases cannot be determined at this time, but it seems noteworthy that the incidence of duplex kidney in this group of cases was 7 per cent, which seems unusually high.

Four patients had evidence of chronic pyelonephritis obtained either by positive culture and pus cells in the kidney urine, or by the finding of abnormal pyelograms with fragmented pelves of the type so commonly seen in chronic pyelonephritis. Only one of these cases had an associated antecedent history of pyelitis with pregnancy.

Two patients had had previous operations on one kidney, being pelviolithotomies in both instances. In one patient in whom the pelviolithotomy had been done here, the blood pressure at the time of operation was recorded as normal.

Finally, there were two cases with a history of rupture of the kidney. A recent case which came under our observation was a young man about twenty-six years of age who was admitted with the typical findings of intracapsular rupture of the kidney associated with rather profuse hematuria over a period of eleven days. Conservative management was adopted and no operation was performed. However, during his stay in the hospital, the blood pressure mounted to as high as 160/100, but gradually subsided as the bleeding ceased, and he improved.

The possible relationship between renal trauma and hypertension at least is indicated by these two cases and parallels a case reported by Nesbit and Ratliff[19], in which hypertension developed some months following rupture of the kidney. Removal of this kidney resulted in a temporary lowering of the blood pressure which, however, ultimately again became elevated although not to the original level.

The importance of these twenty-four patients cannot be assessed, but it is notable that they constituted 33 per cent of the total number of cases studied, which makes them statistically significant. Although no etiological relationship is definitely assigned to this group of cases, future investigations may reveal their true significance.

After considering those patients with hypertension who had associated unilateral kidney disease, it was felt desirable to investigate a similar number of patients who had had nephrectomy for known unilateral kidney disease in order to estimate the incidence of hypertension. Accordingly, the records of seventy-three such cases were studied, which included cases of calculous disease of the kidney or ureter, hydronephrosis with or without infection, pyonephrosis, and a few cases of renal tuberculosis. Of this entire group, only two patients had hypertension, the hypertensive level being arbitrarily placed at 150 mm. of mercury systolic pressure. It thus is apparent that not all cases of unilateral disease have hypertension, and it introduces a problem as to what factors are present to produce hypertension in some cases and not in others. Certainly, from existing evidence, this cannot be answered at this time, but to theorize momentarily, it would seem logical to suppose that the production of hypertension is dependent upon arterial occlusion by inflammation or other pathological processes present in the kidney. Certainly, if one is to accept the Goldblatt principle for all cases, he must believe that the question of whether or not hypertension is present is dependent upon whether or not arterial obstruction is present. Is it not possible, then, that in two groups of patients with similar disease in the kidney one may have arterial occlusion and the other may not?

Deductions and Conclusions

It is thus seen in this study of a group of cases of hypertension that there is a rather high incidence of patients who have evidence of unilateral kidney disease. The percentage of cases seems too high to be coincidental and the etiological relationship at least is suggested.

In the seven cases operated upon, nephrectomy was done primarily because it was indicated on the basis of the existing disease and not because of the hypertension. Even so, there was a definite decrease in blood pressure in four patients, in two of which it returned to normal levels and has remained there.

Finally, *nephrectomy is not being recommended for hypertension.* Nephrectomy must be done *only* when indicated by the existing disease in the kidney and yet bids well to relieve an associated hypertension in a considerable number of patients.

It does seem worthwhile, however, to carry out careful urological investigation in patients with hypertension, for in a certain small pro-

portion it may be found to be caused by a unilateral renal lesion, removal of which will favorably influence the elevated blood pressure. If we can in this way relieve even a small per cent of patients with hypertension, much will have been accomplished in this otherwise rather hopeless group of cases.

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THE TREATMENT OF PNEUMONIA

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Spontaneous recovery from pneumococcic pneumonia depends upon the production by the body of sufficient specific antibodies to unite with all of the pneumococcus antigen (the capsular carbohydrate). This union of antibodies and antigen sensitizes the pneumococci so that they can be destroyed by phagocytosis or lysis. There are two methods of treatment of pneumonia by which the immunological processes of the body can be assisted in attaining a concentration of specific antibodies sufficient to bring about recovery of the patient. One of these consists of the intravenous administration of type-specific antipneumococcus serum, and the other is the method of chemotherapy. Antipneumococcus serum augments the supply of naturally formed antibodies and thus hastens arrival at the stage where antibodies are present in excess of the antigen or capsular carbohydrate. The newer chemotherapeutic agents, on the other hand, act by retarding the multiplication of the pneumococci. The production of antibodies proceeds at its normal rate and, in successfully treated cases, the autogenous supply of antibodies rapidly attains a concentration sufficient to unite with all of the retarded supply of antigen.

Both serum therapy and chemotherapy have proved effective in greatly reducing the mortality rate of pneumococcic pneumonia. With serum therapy the average mortality rate is now approximately 15 per cent; with chemotherapy it is 6 to 8 per cent. Although chemotherapy has a distinct statistical advantage, serum therapy has not been superseded. Further developments in chemotherapy may entirely supplant the use of antipneumococcic serum but, in the meantime, much work must be done concerning the effectiveness of combined treatment with serum and chemotherapeutic agents.

Sulfapyridine and sulfathiazole appear to be equally effective in the treatment of pneumococcic pneumonia, but sulfapyridine causes a more abrupt fall in temperature than does sulfathiazole. Flippin, Schwartz and Rose[1] observed a critical drop in temperature within twenty-four hours in 66 per cent of patients treated with sulfapyridine and in 50 per cent of patients treated with sulfathiazole. In 32 per cent of the patients treated with sulfathiazole, however, crisis did not occur until after seventy-two hours, while it was delayed to this extent in only 13 per cent of the patients who received sulfapyridine. The average duration of hospital care was the same in the two groups of patients.

Nausea and vomiting are more common in patients treated with sulfapyridine than in those who receive sulfathiazole. Drug rashes result more frequently from sulfathiazole than from sulfapyridine. Pepper and Horack[2] demonstrated that sulfathiazole recrystallizes in the kidney

tubules, whereas sulfapyridine usually crystallizes in the renal pelves and ureters. They believe that the renal complications following the use of sulfathiazole will be more serious than those from sulfapyridine. Hepatitis, granulocytopenia, agranulocytosis and hemolytic anemia are rare complications of sulfapyridine therapy and apparently occur even less frequently after the use of sulfathiazole. Before a final decision can be reached concerning the relative merit of the two drugs, both preparations must be studied more thoroughly.

Sulfapyridine and sulfathiazole are administered by mouth, and the sodium salt of both drugs can be given by intravenous injection in 5 per cent solution. The initial oral dose of either preparation usually is 2 grams, and additional doses of 1 gram each are given at intervals of four hours, day and night. The optimum concentration of either drug in the blood is approximately 5 mg. per 100 cc. but favorable responses have been observed with lower concentrations. Treatment is continued until the temperature has returned to normal and has remained there for forty-eight hours. When it is necessary to administer the sodium salt of either drug by intravenous injection, because of severe nausea and vomiting or for some other reason, the usual dose is 2 to 4 grams. Subsequent injections can be given daily or more often, according to the concentration of the drug in the blood.

The development of certain of the manifestations of drug toxicity should be taken as an indication for stopping either sulfapyridine or sulfathiazole. Leukopenia with granulocytopenia, agranulocytosis, acute hemolytic anemia, hematuria, anuria, dermatitis, conjunctivitis, and drug fever are principal contraindications for further use of the preparations. The appearance of any of these conditions calls for the vigorous forcing of fluids in order that the drug may be eliminated from the body as quickly as possible. Transfusions are advisable whenever severe anemia develops. It may be difficult to distinguish between drug fever and fever due to the pneumonia. Long and his coworkers[3] pointed out, however, that drug fever occurs most commonly from the fifth to the ninth day of therapy while patients who have received adequate treatment for pneumonia usually have a normal temperature long before this. The reappearance of fever in a patient whose clinical course is otherwise satisfactory suggests that the fever is due to the drug.

During the time that sulfapyridine or sulfathiazole is being administered, daily measurements should be made of the concentration of the drug in the blood. Failure of the drug to produce a satisfactory response may be due to inadequate absorption from the gastro-intestinal tract, and in a situation of this kind, the intravenous administration of the sodium salt is called for. Severe disturbances of the blood picture seldom occur early in the course of treatment but complete blood counts

should be made daily after the third or fourth day. The urine should be examined for blood each day.

Although the first measure to be employed in the treatment of pneumonia is the administration of sulfapyridine or sulfathiazole, the typing of cases of pneumococcic pneumonia by the Newfeld reaction should not be neglected. There are cases in which, in addition to chemotherapy, serum therapy should be instituted promptly, and this, of course, is impossible unless the type of the invading pneumococcus is known. Combined therapy is advisable in patients who are seriously ill when first seen or who are found to have a positive blood culture, as well as in elderly individuals and in pregnant women. It is also indicated in patients who are unimproved after forty-eight hours of treatment with sulfapyridine or sulfathiazole, in spite of a satisfactory concentration of the drug in the blood. Unfortunately, in the latter group, the delay in serum administration obviously places serum therapy at a distinct disadvantage.

Antipneumococcus serum prepared from horses or rabbits may be obtained for all of the numerically most important types of pneumococci. The serums are now highly refined so that most of the reaction-producing factors have been eliminated. Rabbit serum has the advantage of being more quickly and economically produced and of greater concentration. Moreover, fewer people are sensitive to rabbit serum than to the serum of horses. Before serum of any kind is given, however, a history should be taken concerning such manifestations of allergy as asthma, hay fever, and hives as well as with reference to the previous use of either rabbit or horse serum. In addition, the conjunctival test for serum sensitivity, and if this is negative, the intravenous test should be carried out. If these tests reveal evidence of serum sensitivity, serum therapy should be employed only in urgent situations. The serum should be well diluted with sterile physiologic salt solution and should be given very slowly.

There is still some difference of opinion as to whether or not the total dose of antipneumococcus serum should be given in a single injection or in several injections at intervals of one or two hours. Practically all workers agree, however, that the total estimated dose should be administered within the first twelve hours of treatment. The usual dosage employed is 100,000 units for all types of pneumonia except types II and III, and 200,000 units for types II and III. In the case of elderly individuals and in those with involvement of more than one lobe, these amounts may be doubled. After the amount decided upon has been administered, it usually is best to wait for twelve hours before considering the use of additional serum.

Although the modern treatment of pneumonia has greatly simplified

the problem of general care of the patient, there are certain principles that must be kept in mind. The patient should be isolated and every measure should be taken to insure physical and mental rest. Adequate nursing care is essential; the position in bed should be as comfortable as possible and should be changed as necessary. Fluids should be given at frequent intervals and in amounts sufficient to keep the twenty-four hour volume of urine up to 1500 cc. In seriously ill or delirious individuals and in those who are greatly troubled with nausea and vomiting, it will be necessary to administer 5 per cent glucose in physiologic salt solution in order to maintain this level of urine output. The diet may be liquid or soft, depending upon the general condition of the patient. Prompt treatment of the pneumonia and the use of a cleansing enema as necessary are the two most effective measures in the prevention of distention. Codeine may be necessary for cough, and severe pain will at times necessitate the use of morphine. A many-tailed bandage often is very helpful in relieving less severe pleural pain. Sedatives should be given at night to secure restful sleep. Digitalis is administered only in the event that auricular fibrillation or evidence of congestive heart failure develops.

Because of the greatly shortened course of pneumonia treated successfully with sulfapyridine or sulfathiazole, the administration of oxygen is necessary much less frequently than formerly. Oxygen therapy has not diminished in value, however, and should be employed, preferably by means of an oxygen tent, whenever there is cyanosis, undue tachycardia, shallow respiration with a rate above 40 per minute, or great restlessness and delirium.

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CONTRIBUTORS

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